

Prevalence of Opportunistic Infection in Central Nervous System among Patients with HIV/AIDS at Dr. Hasan Sadikin General Hospital Bandung, Indonesia

Dinda Sayyidah Laela Fatimatuzzahra,¹ Ahmad Rizal Ganiem,² Aih Cahyani,² Suryani Gunadharma,² Sofiati Dian²

¹Faculty of Medicine Universitas Padjadjaran, Indonesia, ²Department of Neurology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Background: The low coverage of diagnosis and treatment in patients with human immunodeficiency virus (HIV) infection in Indonesia increases the risk of opportunistic infections that affects various organs, including the central nervous system (CNS). This study aimed to determine the prevalence of opportunistic infections in the CNS among hospitalized patients with HIV/acquired immune deficiency syndrome (AIDS) at Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

Methods: In this cross-sectional study with a total sampling method, data were collected from HIV/AIDS patients who were diagnosed with CNS opportunistic infection and hospitalized in the neurology ward during the period 2015–2019. Data were presented as median (interquartile range) and percentage frequency.

Results: Among the 2,606 HIV/AIDS patients registered, 219 (8.4%) were accompanied by CNS opportunistic infections. The highest number was cerebral toxoplasmosis (58.9%; n=129) followed by tuberculous meningitis (33.3%; n=73) and cryptococcal meningitis (7.8%; n=17). Most of the patients admitted for unconsciousness (64.4%; n=141), with unknown HIV-infection status (61.2%; n=134). Among patients with positive HIV-infection status, only 50.6% (43/85) patients were taking antiretroviral therapy (ART) and 24.7% (21/85) patients dropped out ART before being diagnosed with CNS opportunistic infections. The CD4+'s median value was 21 cells/mm³ (IQR 9-61.25), with mortality during hospitalization was 36.5% (80/219).

Conclusions: The prevalence of CNS opportunistic infections among HIV-infected patients is 8.4%, dominated by cerebral toxoplasmosis, and laboratory result showed very low CD4+ levels. The diagnosis of HIV infection is shortly made before hospitalization, and those who has been diagnosed have low compliance with ART. The mortality rate during hospitalization is high.

Keywords: AIDS, CNS opportunistic infections, prevalence

Introduction

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is a major global public health issues, including in Indonesia.¹ In 2018, it was estimated around 640,000 people were infected with HIV, but only 51% (327,000) people knew their infection status, and only 17% (108,000) people received antiretroviral therapy (ARV) in Indonesia.² Delayed diagnosis due to uninformed and limited medical services and

also low coverage of ARV have caused many patients to visit the hospital at the late stage of the disease with very low CD4+ cells, and are frequently hospitalized for opportunistic infections.³

Opportunistic infections are infections of microorganisms that in normal conditions are not virulent enough to cause clinical disease. However, in the immunocompromised host, these microorganisms can cause clinical disease.⁴ Opportunistic infections can occur in various organs of the system, including

Correspondence: Dinda Sayyidah Laela Fatimatuzzahra, Faculty of Medicine Universitas Padjadjaran, Jalan Raya Bandung Sumedang Km. 21 Jatinangor, Sumedang Indonesia, E-mail: dinda17010@mail.unpad.ac.id

the central nervous system (CNS). CNS opportunistic infections include tuberculous meningitis, cryptococcal meningitis, cerebral toxoplasmosis, cytomegalovirus (CMV) encephalitis, and progressive multifocal leukoencephalopathy (PML).⁵ These diseases can cause tissue damage and leads to death, so it is important to make a correct and fast diagnosis in the order to get appropriate management that will improve patient outcome.⁶

There are limited data regarding the prevalence of CNS opportunistic infections in HIV/AIDS patients in West Java. Therefore, a study at Dr. Hasan Sadikin General Hospital Bandung, the main referral hospital in West Java, is important to conduct. The aim of this study was to determine the prevalence of CNS opportunistic infections in HIV/AIDS patients at Dr. Hasan Sadikin General Hospital, Bandung. This study is expected to represent data from West Java entirely, moreover will be useful in Indonesia, as West Java is the largest populated province in Indonesia.⁷ Furthermore, the results of this study can become an insight for health workers related to the burden of diseases and increasing early detection so that complications can be prevented and improve patient outcomes.

Methods

This study was a descriptive retrospective with a cross-sectional study design using secondary data. The subjects of this study were HIV/AIDS positive patients who were hospitalized at the Department of Neurology Dr. Hasan Sadikin Bandung from 2015 to 2019. Inclusion criteria were patients diagnosed with CNS opportunistic infections related to HIV/AIDS. Missing data were excluded. Data collected from August to November 2020. This study was approved by the Research Ethics Committee Universitas Padjadjaran number: 735/UN6.KEP/EC/2020.

Data were collected and categorized based on research variables, including diagnosis of CNS opportunistic infections such as tuberculous meningitis, cryptococcal meningitis, cerebral toxoplasmosis, cytomegalovirus (CMV) encephalitis, and progressive multifocal leukoencephalopathy (PML). Other variables were gender, age, chief complaint, the HIV status before current hospitalization. Those who knew their HIV status were checked for the duration of HIV/AIDS, and the status of using ARV. The blood count data, hemoglobin, leukocytes, differential count, platelets, as

well as the CD4+ count were taken from the medical record. The hospitalization outcome was also noted.

Data were analyzed with descriptive statistics using the IBM SPSS version 25. Data were analyzed with a normality test and continued with a number (n), proportion (%), median and interquartile range (IQR).

Results

During 2015–2019, there were 2,606 HIV/AIDS patients hospitalized at Dr. Hasan Sadikin Bandung, 242 of whom had CNS opportunistic infections, including 23 relapse cases that were excluded. The prevalence of CNS opportunistic infections was 8.4% (219/2,606). There were 199/209 patients (95.2%) who had one opportunistic infection and 10/209 patients (4.8%) who had two opportunistic infections. Patients who had two opportunistic infections consisting of cerebral toxoplasmosis and tuberculous meningitis (9/10; 90%) and then tuberculous meningitis and cryptococcal meningitis (1/10; 10%) as shown in Table 1.

The CNS opportunistic infections recorded in 219 cases, consisted of cerebral toxoplasmosis in 129 cases (58.9%), tuberculous meningitis in 73 cases (33.3%), and cryptococcal meningitis in 17 cases (7.8%). There were no records of patients hospitalized with other opportunistic infections (Table 2).

The median age of the patients was 33 years (IQR 26–39) and mostly male, 160/219 (73%). Patients presented with decreased consciousness (64.4%), headache (17.4%), seizures (8.2%), weakness of the limb (7.3%), speech disturbances (1.4%), and behavioral change (0.4%) as a chief complaints.

Only 85 patients (38.8%) had known their HIV infection status before arrival, with a median duration of HIV infection being 5 months (IQR 2–36). Among the 85 patients, there were 43 patients (50.6%) currently using ARV, 21 patients (24.7%) had never used ARV and 21 patients (24.7%) had dropped out from ARV. Of the 21 patients who dropped out from ARV, 19 patients (90.5%) stopped due to their compliance, and 2 patients (0.5%) due to side effects such as nausea, vomit, and skin hyperpigmentation. The CD4+ examination was performed in 134 patients (61%) and median was 21 cells/mm³ (IQR 9–61.25).

Routine blood tests were performed in all patients, but differential count data was only available in 56 patients (26%). From these tests, hemoglobin median was 11.6 g/dL (IQR 9.88–13.3), leukocytes 7060 cells/mm³ (IQR

Table 1 Distribution of Opportunistic Infection in the Central Nervous System among Patients Hospitalized (n=2,606) in Dr. Hasan Sadikin Bandung during 2015–2019

Number of CNS Opportunistic Infection Diagnoses	Number of Patients (n)	Proportion n/N=x (%)
One opportunistic infection	199	95.2
Two opportunistic infections	10	4.8
Total	209	100

4700–9785), platelets 242 thousand cells/mm³ (IQR 173–309). Differential count examination showed median for basophils and band neutrophils were 0% (IQR 0–0), eosinophils were 0% (IQR 0–1), segment neutrophils were 79% (IQR 70–89), lymphocytes were 10% (IQR 5.25–16), and monocytes were 6% (IQR 4–8.75).

During hospitalization, 139 patients survived (63.5%) including 21 discharged patients based on their request and 80 patients (36.5%) died. Patients with the highest mortality rate were tuberculosis meningitis (48%), followed by cryptococcal meningitis (41.2%) and cerebral toxoplasmosis (27.1%).

Patient characteristics for each diagnosis including gender, age, chief complaint, HIV status, routine blood count, and mortality during hospitalization can be seen in Table 3.

Discussions

In this study, it was found that the prevalence of CNS opportunistic infections in HIV/AIDS patients hospitalized at Dr. Hasan Sadikin General Hospital was 8.4%. This number was similar to the study conducted at Cipto Mangunkusumo Hospital, which was 9%.⁸ The most common CNS opportunistic infections were cerebral toxoplasmosis (58.9%)

followed by tuberculous meningitis (33.3%) and cryptococcal meningitis (7.8%). There was no patient with other CNS opportunistic infections. The distribution of these diagnoses among CNS opportunistic infections is consistent with the same as similar studies in the same place (Dr. Hasan Sadikin General Hospital) at different periods (2007–2012) or in several other places.^{9–11}

Patients with CNS opportunistic infections in this study were predominantly male (73%). This may be related to the prevalence of HIV/AIDS patients in Indonesia. In general, male patients of HIV/AIDS are higher than female (>60%).¹² CNS opportunistic infections mostly occurred in the early adult, with a median of 33 years (IQR 26–39). Opportunistic infections usually occur when the patient had entered the AIDS phase, which is 7–10 years from the first exposure to HIV, so it could be estimated that many risk factor behaviors of HIV are done by the young generation in Indonesia.¹³ This age range was a productive age group, so it can become a serious problem of psychological, social, and economic besides their physical problems.¹⁴

Many patients did not know their HIV infection status before being hospitalized due to CNS opportunistic infections. One of the reasons was that HIV infection was

Table 2 Prevalence of Opportunistic Infection in the Central Nervous System among HIV/AIDS Patients hospitalized (n=2,606) in Dr. Hasan Sadikin Bandung during 2015–2019

Diagnosis	Number of Confirmed Diagnoses (n)	Prevalence n/N=x(%)
Cerebral toxoplasmosis	129	58.9
Tuberculous meningitis	73	33.3
Cryptococcal meningitis	17	7.8
PML	-	-
CMV encephalitis	-	-
Total	219	100

Note: PML = Progressive multifocal leukoencephalopathy, CMV= Cytomegalovirus

Table 3 Characteristics of HIV / AIDS Patients with Opportunistic Infections in Central Nervous System, Hospitalized in Dr. Hasan Sadikin General Hospital Bandung during 2015-2019

Characteristic	CT (n=129) n (%)	TM (n=73) n (%)	CM (17) n (%)
Male; n (%)	97 (75.2)	50 (68.5)	13 (76.5)
Age in year - median (IQR)	33 (26-39)	33 (26-39)	31 (28-38)
Knowing the status of HIV before current hospitalization	49 (38)	25 (34.2)	11 (64.7)
Duration of HIV/AIDS diagnosed in months - median (IQR)	4 (2-48)	4 (2-12)	6 (1-36)
Usage of ARV; n(%)	27 (55.1)	13 (52)	3 (27.3)
Ongoing	9 (18.4)	7 (28)	5 (45.4)
Drop-out	13 (26.5)	5 (20)	3 (27.3)
Never			
Chief complain; n(%)	75 (58.1)	60 (82.3)	6 (35.3)
Decreased consciousness	20 (15.5)	7 (9.6)	11 (64.7)
Headache	17 (13.2)	1 (1.4)	-
Seizure	13 (10.1)	3 (4.1)	-
Limb weakness	2 (1.6)	1 (1.4)	-
Speech disturbances	-	1(1.4)	-
Behavioral change	2 (1.6)	-	-
Others			
Laboratory examination			
Hemoglobin in g/dL - median (IQR)	12.2 (10.25-13.55)	10.8 (9.1-12.9)	12.4 (10.62-13.28)
Leucocytes in cells/mm ³ - median (IQR)	7000 (4715-9395)	7110 (4625-10622.5)	7100 (3850-9395)
Differential counts in % -median (IQR)*			
Basophil	0 (0-0)	0 (0-0)	0 (0-0)
Eosinophil	0 (0-1)	0 (0-0)	0 (0-6)
Neutrophil band	0 (0-0.5)	0 (0-0)	0 (0-1)
Neutrophil segment	78 (70-87)	86 (71.5-90.5)	88 (62-91)
Lymphocyte	12 (7-15.5)	10 (4.25-18.25)	6 (5-16)
Monocyte	6 (4-9.5)	5,5 (3-6.75)	6 (4-12)
Platelets in 10 ³ cells/mm ³ -median (IQR)	248 (178-308.5)	237 (170-320.5)	234 (119-296.5)
CD4+ in cells/mm ³ - median (IQR)**	20.5 (9.75-51.5)	29 (6.5-83.5)	16.5 (4-146)
Mortality during hospitalization; n(%)	35 (27.1)	38 (52)	7 (41.2)

Note: CT= Cerebral toxoplasmosis, TM= Tuberculous meningitis, CM= Cryptococcal meningitis, *Differential counts examination was only available in 33 CT patients, 16 TM patients and 7 CM patients, **CD4+ counts was only available in 90 CT patients, 36 TM patients and 8 CM patients

asymptomatic or only mild non-specific at the initial phase, patients did not realize it until the infection became AIDS, which was characterized by the presence of certain opportunistic diseases.¹³ This caused high patients to come with a chief complaint related to their opportunistic infection.

Among the patients who already knew their infection status, the incidence of ARV drop-out was still high and could be related to the high incidence of CNS opportunistic infections. A study showed factors associated with ARV drop-out, including lower CD4+ cell counts and lack of support from family or friends.¹⁵ In Indonesia, there is still discrimination against HIV patients and very low coverage of the HIV treatment cascade.^{2,14} These conditions may

be related to the death number caused by AIDS in Indonesia is still the highest compared to other countries in Southeast Asia.²

The most common chief complaint in this study was decreased consciousness, followed by headache, seizures, and weakness of the limbs. These complaints are very specific complaints about CNS disorders. Other studies showed the clinical manifestations of CNS infection were the same, including headache, decreased consciousness, seizures, limb weakness, fever, nausea, and chronic cough.¹⁰ However, in this study, symptoms such as fever and nausea, were not become chief complaints because of mild and nonspecific symptoms.

HIV-infected patients become AIDS when the CD4+ cell count is ≤ 200 cells/mm³.¹⁶ This

study showed CD4+ median value was 21 cells/mm³ and 95.5% of cases had CD4+ ≤200 cells/mm³. The highest median CD4+ was found in tuberculous meningitis, followed by cerebral toxoplasmosis and cryptococcal meningitis. These findings were the same as the theory that CD4+ is usually lower in cryptococcal meningitis patients compared to tuberculous meningitis and cerebral toxoplasmosis.¹⁷

HIV patients often had abnormalities on blood tests, which also occurred in this study including anemia (78%), lymphopenia (44.6%), leukopenia (18.3%), and thrombocytopenia (15.1%). These results were similar to studies conducted by Subhash et al. Blood abnormalities in HIV patients were caused by immune cell damage, viral cytopathic effects, side effects therapy, and suppression of hematopoiesis.¹⁸

The outcome of death during hospitalization was 36.5%, mostly occurred to tuberculous meningitis (52%), followed by cryptococcal meningitis (41.2%) and cerebral toxoplasmosis (27.1%). This outcome was similar to several other studies.^{19,20}

The limitation of this study is the incomplete data of the study. Data were not available for 5 months of the study period, namely January 2015, February 2015, March 2015, September 2017, and August 2019. Also, there were several incomplete variables, including CD4+ and differential count variables. Future studies are needed to collect the complete data to increase the accuracy of the prevalence study.

In conclusion, the prevalence of CNS opportunistic infections in HIV/AIDS patients hospitalized at Dr. Hasan Sadikin General Hospital in 2015–2019 is 8.4% with the highest case being cerebral toxoplasmosis, which mostly occur in productive age and very low CD4+ cell levels (<100 cells/mm³). Many of these patients do not know their HIV infection status when they come with complaints of CNS opportunistic infections. The drop-out ART rates before diagnosis of CNS opportunistic infections and deaths during treatment are still high. Therefore, earlier diagnosis and antiretroviral treatment are compulsory to control the disease progressivity characterized by opportunistic infections including CNS opportunistic infections.

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