RESEARCH

Presentation, etiology, and outcome of brain infections in an Indonesian hospital

A cohort study

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Abstract

Background

Little detailed knowledge is available regarding the etiology and outcome of CNS infection, particularly in HIV-infected individuals, in low-resource settings.

Methods

From January 2015 to April 2016, we prospectively included all adults with suspected CNS infection in a referral hospital in Jakarta, Indonesia. Systematic screening included HIV testing, CSF examination, and neuroimaging.

Results

A total of 274 patients with suspected CNS infection (median age 26 years) presented after a median of 14 days with headache (77%), fever (78%), seizures (27%), or loss of consciousness (71%). HIV coinfection was common (54%), mostly newly diagnosed (30%) and advanced (median CD4 cell count 30/μL). Diagnosis was established in 167 participants (65%), including definite tuberculous meningitis (TBM) (n = 44), probable TBM (n = 48), cerebral toxoplasmosis (n = 48), cryptococcal meningitis (n = 14), herpes simplex virus/varicella-zoster virus/cytomegalovirus encephalitis (n = 10), cerebral lymphoma (n = 1), neurosyphilis (n = 1), and mucormycosis (n = 1). In-hospital mortality was 32%; 6-month mortality was 57%. The remaining survivors had either moderate or severe disability (36%) according to Glasgow Outcome Scale.

Conclusion

In this setting, patients with CNS infections present late with severe disease and often associated with advanced HIV infection. Tuberculosis, toxoplasmosis, and cryptococcosis are common. High mortality and long-term morbidity underline the need for service improvements and further study.

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CNS infections cause considerable morbidity and mortality,[1] especially in low and middle income countries, where HIV infection remains more prevalent, putting people at higher risk for CNS infections. Establishing a diagnosis may be more challenging in low-resource settings, as lumbar punctures are not always done, access to advanced molecular diagnosis and neuroimaging is often limited, and specific drugs or IV formulations may not be available.

These challenges are especially relevant in Indonesia, the fourth most populous country in the world. As Indonesia has the second fastest growing HIV epidemic in Asia,[2] the burden of CNS infections is also likely to expand. Previous studies have focused on selected infections, especially tuberculous meningitis (TBM),[3,4] cryptococcal meningitis, and cerebral toxoplasmosis,[5,6] but the relative distribution and patterns of different pathogens, and their clinical presentation and outcome, remain unknown. We therefore performed a prospective cohort study in the largest referral hospital in Indonesia, to examine the etiology, clinical characteristics, treatment, and outcome of CNS infections in adults, in HIV-infected and uninfected patients. The findings will help to improve diagnostic algorithms and clinical management of patients with suspected CNS infections in Indonesia and comparable settings elsewhere.

Methods

Setting, patient population, and study design

We conducted a prospective cohort study in Cipto Mangunkusumo Hospital, a government university hospital that serves the local community and acts as a tertiary referral hospital for Indonesia. From January 2015 to April 2016, all consecutive patients over 16 years of age with clinically suspected CNS infection (according to clinical judgement of the attending neurologists) were included. Systematic history taking, physical and neurologic examination, CSF and blood examinations, and reading of brain CT and chest X-ray were done. CSF and blood samples were archived for further testing. All patients with a confirmed or presumptive diagnosis of CNS infection were followed prospectively for 6 months.

Standard protocol approvals, registrations, and patient consents

Approval from the ethics committee of the Faculty of Medicine, Universitas Indonesia, has been received for this study (764/UN2.F1/ETIK/2014) and written informed consent for bioarchiving of samples was obtained from all patients (or guardians of patients) participating in the study.

Clinical and radiologic examination

As per routine clinical care, patients with clinically suspected CNS infections in this hospital usually receive a CT scan of the brain with IV contrast. With patient consent, a large volume (10 mL) of CSF is collected by lumbar puncture, unless there is circulatory shock, severe thrombocytopenia, or brain herniation. Standard CSF measurements comprised microscopic and biochemical analysis, plus microbiological tests selected on a case-by-case basis. Routine blood examination consists of complete blood count and leukocyte differentiation, random blood glucose, sodium, creatinine, and liver enzymes. Neurosurgical interventions (e.g., ventricular drainage) are not routinely available for patients with CNS infections. All patients with suspected CNS infections are routinely tested for HIV, using a provider-initiated testing and counseling approach, in line with national and hospital policies. CD4 cell counts are routinely performed for all HIV-infected persons, and antiretroviral treatment (ART) is provided free of charge to all symptomatic patients or those with CD4 cell counts below 350 cells/μL in accordance with national guidelines.

For this cohort, patient data were captured using an electronic data capture system (REDCap).[7] All patients and their relatives were questioned to assess signs and symptoms, medical history, medication use, possible risk factors, and sociodemographic characteristics. Physical examination included Glasgow Coma Scale and neurologic examination performed by a certified neurologist. CSF was used for first-line microbiological examinations; CSF and serum were archived for second-line diagnostics (as described in detail below).

Brain CT scans were performed using a dual-source 128-slice Siemens (Erlangen, Germany) SOMATOM Definition Flash CT scan. The images were scored by a single experienced radiologist for the presence of meningeal enhancement, infarction, hydrocephalus, abscess, tuberculoma, herniation, and encephalitis. Meningeal enhancement was defined as enhancement of the pia mater that could extend into the subarachnoid spaces, particularly the cerebral sulci and cisterns. Infarction was defined as a hypodense lesion with or without contrast enhancement within a certain vascular territory. Hydrocephalus was defined as enlargement of the ventricles particularly with stretching and upward displacement of the corpus callosum, widening of third ventricular recesses, and decreased mammillopontine distance. Abscess was defined as space-occupying lesion with smooth inner and outer margin capsular ring contrast enhancement. Tuberculoma was defined as solitary or multiple isohyperdense lesion with ring enhancement or an area of nodular or irregular nonhomogenous enhancement. Herniation was defined as shifting of cerebral tissue from its normal location into an adjacent space as a result of mass effect. Encephalitis was defined as hypodense lesion with focal brain edema. In addition to the CT scan, chest radiographs were examined and abnormalities were classified as miliary, infiltrative, cavitary, or other signs suggestive of pulmonary tuberculosis.

Laboratory testing and diagnosis

Routine CSF measurements included leukocyte counts, protein, glucose, and microscopic examination using Ziehl-Neelsen (ZN) staining, Gram staining, and India ink. For this study, specifically for tuberculosis diagnosis, 5–10 mL CSF was centrifuged at 3,000 *g* for 15 minutes, and 100 μL sediment was used for ZN staining, 100 μL for culture (BD MGIT 960 Mycobacteria Culture System), and 200 μL for nucleic acid amplification test (Xpert MTB/RIF). The supernatant was

then stored at −80°C. For individual patients, physicians requested CSF PCR for herpes simplex virus, varicella-zoster virus, culture and microscopy for fungal infections, and cytology for diagnosis of primary CNS lymphoma.

Secondary, batch-wise testing was done on archived CSF and blood samples for those patients for whom no diagnosis was made on primary testing. Batch-wise testing for HIV-negative patients include tests for arboviral infections (using flavivirus reverse transcriptase [RT]–PCR and sequencing, dengue RT-PCR,[8] alphavirus RT-PCR and sequencing,[9] anti-JE immunoglobulin M [IgM] ELISA, anti-dengue IgM ELISA,[10] and virus culture), enteroviral infection using PCR,[11] herpesvirus encephalitis using herpes simplex virus–1 PCR,[12] and NMDA encephalitis using CSF anti-NMDAR antibodies. Meanwhile, batch-wise testing for HIV-infected patients included neurosyphilis assays, cerebral toxoplasmosis, cytomegalovirus encephalitis, and cryptococcal meningitis.

Initial diagnoses to guide empiric treatment were made by the treating physician. Final diagnoses were made by consensus using predefined criteria based on primary and secondary analyses (table 1).

Treatment and follow-up

Treatment was at the discretion of treating physicians. Decisions regarding empiric treatment for suspected tuberculosis, bacterial meningitis, cerebral toxoplasmosis, and herpes encephalitis were based on clinical judgement, routine CSF testing, and CT scan, without available

Table 1 Predefined diagnostic criteria

Diagnosis	Explanation	Reference
TBM	Definite: positive CSF microscopy for acid-fast bacilli, *Mycobacterium tuberculosis* culture, or PCR (Xpert TB)	22
	Probable: TBM research case definition score ≥10 (without available CT imaging) or ≥12 (with CT), and exclusion of alternative diagnoses	22
	Possible: TBM research case definition score of 6–9 points (without available CT imaging) or 6–11 points (with CT), and exclusion of an alternative diagnosis	22
Cerebral toxoplasmosis	Definite: HIV infection and 1 or more cerebral mass lesions on CT or MRI and a positive CSF *Toxoplasma* PCR and a documented clinical response to antitoxoplasmosis treatment (i.e., discharged alive), and exclusion of an alternative diagnosis	23
	Presumptive: HIV infection and presence of 1 or more cerebral mass lesions on CT or MRI and a documented clinical response to antitoxoplasmosis treatment (i.e., discharged alive), and exclusion of an alternative diagnosis	23
Cryptococcal meningitis	Positive CSF India ink examination (budding encapsulated yeasts), or *Cryptococcus neoformans* culture, or cryptococcal antigen lateral flow antigen test	15
CMV, HSV, and VZV viral encephalitis	Positive CSF PCR for HSV, CMV, or VZV and altered mental status plus 2 or more of the following: fever ≥38°C; seizures; new onset of focal neurologic findings; CSF WBC count ≥5/mm^3; abnormality of brain parenchyma on neuroimaging suggestive of encephalitis	24
Encephalitis of unknown etiology	Altered mental status plus 2 or more of the following: fever ≥38°C; seizures; new onset of focal neurologic findings; CSF WBC count ≥5/mm^3; abnormality of brain parenchyma on neuroimaging suggestive of encephalitis (with negative CSF virologic examination)	24
Bacterial meningitis	Definite: meningitis with detection of bacteria in CSF by microscopy or culture	25
	Probable: compatible clinical syndrome, positive blood culture, plus 1 of the following CSF changes: >5 leukocytes/mm^3; glucose <40 mg/dL or CSF/blood glucose ratio <0.5; or protein >100 mg/dL	26
	Possible: compatible clinical syndrome, plus one of the following CSF changes: >100 leukocytes/mm^3; glucose <40 mg/dL or CSF/blood glucose ratio <0.5; or protein >100 mg/dL plus negative cultures or antigen for bacteria, viral, fungal, or mycobacteria	26
Neurosyphilis	Reactive CSF VDRL and elevated CSF cell count plus exclusion of alternative diagnoses	27
CNS infection of unknown etiology	Suspected CNS infection based on combination of compatible clinical signs, CSF findings, and brain CT scan with no other diagnoses	Consensus
No suspicion of CNS infection	Confirmed alternative diagnosis (e.g., brain tumor) or no suspicion of CNS infection based on clinical signs, CSF findings, and CT scanning	Consensus

Abbreviations: CMV = cytomegalovirus; HSV = herpes simplex virus; TBM = tuberculous meningitis; VDRL= venereal disease research laboratory; VZV = varicella-zoster virus; WBC = white blood cells.

microbiological results. Drug regimens and doses were in agreement with prevailing guidelines. As per routine care, suspected TBM in this hospital is treated empirically with a combination of rifampicin (600 mg), isoniazid (300 mg), ethambutol (750 mg), and pyrazinamide (1,500 mg). Patients with reduced level of consciousness receive their drugs by nasogastric tube. All TBM patients are given adjunctive dexamethasone for 6–8 weeks in a tapering dose. Suspected bacterial meningitis is treated with ceftriaxone IV 2–4 g/d for 10–14 days with administration of IV dexamethasone 20 mg/d for 4 days. Clinically suspected herpes encephalitis is treated with IV acyclovir 10 mg/kg/d for 7–14 days. Suspected cerebral toxoplasmosis is treated with pyrimethamine 50–75 mg and clindamycin 2,400 mg daily for 2–4 weeks. Confirmed cryptococcal meningitis is treated with IV amphotericin B (0.7–1 mg/kg bodyweight) combined with oral fluconazole at a starting dose of 800 mg/d for 2 weeks; flucytosine is not available in Indonesia. For cytomegalovirus encephalitis, some patients received IV ganciclovir 5 mg/kg/d every 12 hours for 2 weeks.

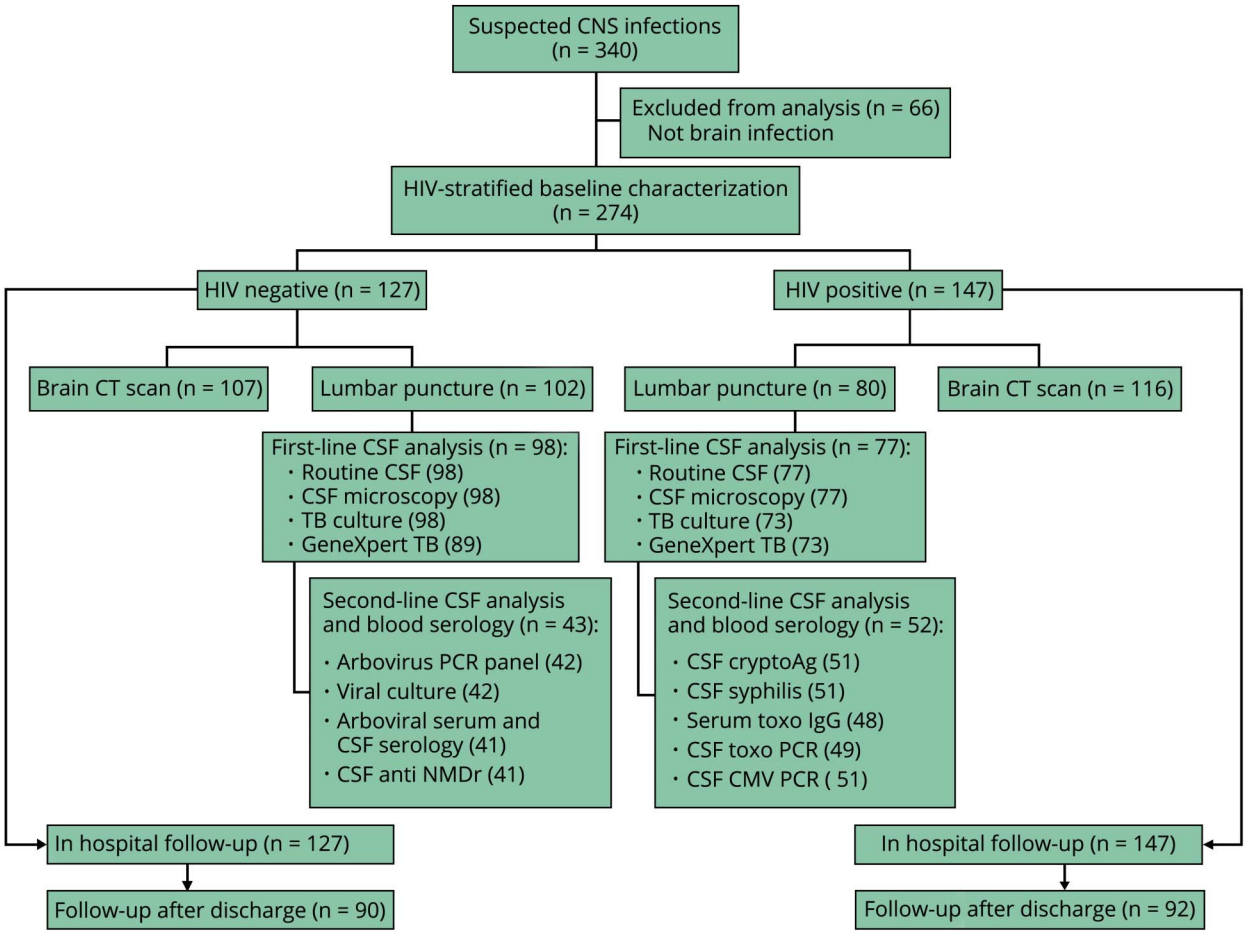
In accordance with national guidelines, ART in this hospital consists of once daily efavirenz 600 mg, tenofovir 300 mg, and lamivudine 300 mg, and lopinavir/ritonavir plus optimized nucleoside reverse transcriptase inhibitor backbone as second-line therapy. For patients with newly diagnosed HIV infection, ART is generally started 2–8 weeks after start of treatment of CNS infections (earlier in TBM and toxoplasma encephalitis, later in cryptococcal meningitis).

To avoid transfer bias in monitoring survival after hospital discharge, patients were followed using medical records of routine outpatient clinic visits and phone calls or home visits for those not attending to scheduled visits. The Glasgow Outcome Scale (GOS) was used to evaluate neurologic outcomes. GOS is a scale for functional outcome that rates patient into one of 5 categories: dead, vegetative state, severe disability, moderate disability, or good recovery.

Data analysis and statistics

Baseline patient characteristics were expressed using proportion (%), median, and interquartile range (IQR). Comparisons between groups were done using χ^2 and parametric or nonparametric tests as appropriate. Kaplan-Meier curves were used to illustrate survival according to HIV status and baseline clinical measures. Continuous measures were

Figure 1 Patients presenting with suspected CNS infection



CMV = cytomegalovirus; IgG = immunoglobulin G; TB = tuberculosis.

divided into 3 groups with cutoffs allowed to deviate slightly from exact tertiles to improve interpretability of results. Univariate and multivariate regression analyses were done to identify clinical, laboratory, or radiologic predictors of 1- and 6-month mortality. Analyses were stratified according to HIV status. All statistical analyses were performed using SPSS 17 for Windows (SPSS Inc., Chicago, IL).

Participants with missing data were omitted from the statistical analysis. Participants with loss to follow-up were censored from the analysis.

Data availability

Any data not published within the article will be shared by request from the corresponding author.

Results

Clinical presentation

During the study period, a total of 340 patients presented with suspected CNS infection. Sixty-six patients were excluded from analysis because of alternative diagnoses (n = 56), like sepsis, brain tumor, stroke, epilepsy, and primary headache, or incomplete data (n = 10; figure 1). Of the 274 patients who were included in further analysis, 249 were admitted via the emergency department (91%), either as self-referrals (61%) or from other hospitals (30%), and 25 (9%) were included as inpatients in the medical or pulmonary ward. Patients presented after a median of 14 days (IQR 7–30) of neurologic symptoms, with severe disease manifestations including seizures (27%), motor abnormalities (42%), cranial nerve palsy (39%), and altered mental status (70%).

HIV infection was present in 147 (54%) patients, including 83 who were unaware of their HIV status prior to their current hospitalization. Among those with a previously diagnosed HIV infection, 32 (50%) had a history of ART use and 27 patients (42%) were on cotrimoxazole *Pneumocystis* pneumonia prophylaxis. The median CD4 cell count was 29/μL (range 0–611/μL) among patients with previously diagnosed and 30/μL (range 3–694/μL) among those with newly diagnosed HIV infection. Compared to those without HIV, HIV-infected patients were more often male, and more often presented with motor abnormalities, but less frequently with loss of consciousness (table 2).

Lumbar punctures were done in 182 patients (67%), more often in HIV-negative (80%) compared to HIV-positive (54%) patients (figure 1). No lumbar puncture was performed in 92 patients, mainly because of a doctor's decision (n = 68), most often because of the presence of mass lesions or brain herniation. Thirteen patients refused lumbar puncture, while for 11 patients no reason could be verified for the fact that no lumbar puncture was done. CSF examination mostly showed mild pleiocytosis, with a predominance of mononuclear cells, elevated protein, and low glucose (table 2). CT scan, performed in 223 patients (81%), showed abnormalities in 181 (81%), with meningeal enhancement and encephalitis as the most common findings. Mass lesions, brain herniation, and encephalitis/cerebritis were more common among HIV-infected patients, while hydrocephalus was more common in HIV-noninfected patients. Based on clinical presentation, CSF, and CT scan findings, 47 (17%) patients presented with a clinical picture resembling encephalitis (with seizures and behavioral changes), and 133 patients (49%) with meningitis (with meningismus

Table 2 Patient characteristics stratified by HIV status

	HIV-positive (n = 147)	HIV-negative (n = 127)	*p* Value
Male sex	77	54	<0.001
Age, y	32 (29–39)	32 (25–43)	0.49
New HIV diagnosis	57	—	
History			
Duration of first neurologic symptoms, d	14 (7–30)	10 (3–21)	0.013
History of fever	78	79	0.91
Headache	78	79	0.26
Vomiting	31	29	0.79
Chronic cough	29	24	0.35
Loss of consciousness	65	77	0.023
Seizures	25	30	0.38
Behavioral changes	23	28	0.32
Physical examination			
Body temp <37.5°C	28	24	0.4
Glasgow Coma Scale score	13 (10–15)	13 (10–14)	0.15
Cranial nerve palsy	42	35	0.2
Neck stiffness	44	48	0.53
Motor abnormalities	51	32	0.001
Papilledema	34	24	0.07
CSF[a]			
Leukocytes, cells/UL	18 (6–60)	36 (10–155)	0.024
Polymorphonuclear cells, %	20 (10–60)	20 (10–50)	0.71
Protein, mg/dL	48 (20–129)	55 (20–150)	0.39
CSF:blood glucose ratio	0.49 (0.34–0.62)	0.5 (0.31–0.72)	0.59
Blood			
Hemoglobin, g/dL	11.7 (9.7–13.1)	12.9 (11.4–14.3)	<0.001
Leukocytes, 10^9/L	9.5 (5.3–9.9)	13.0 9.4– (18.1)	<0.001
Thrombocytes, 10^9/L	228 (165–325)	323 (224–402)	<0.001

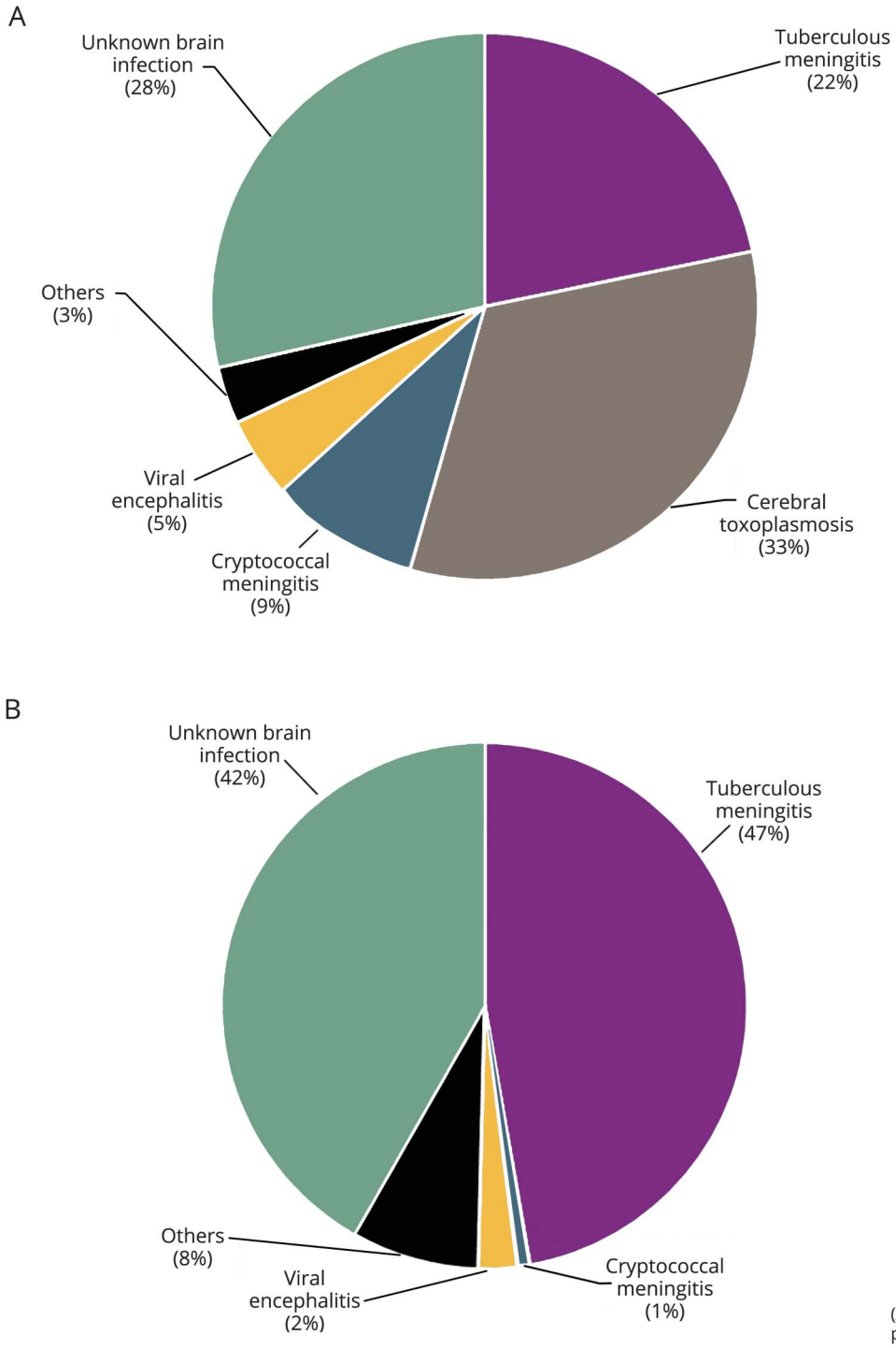
Data are 100% complete for sex, age, and HIV diagnosis; ≥99% complete for history and physical examination; and ≥90% complete for blood examination.
Values are % or median (IQR).
[a] CSF data were obtained from 80 HIV-infected and 102 HIV-noninfected participants.

and typical CSF and CT findings), while for the remainder this distinction could not be made.

Microbiological examination and disease etiology

A definite diagnosis was made in 81 patients (30%), including TBM (n = 44), cerebral toxoplasmosis (n = 10), cryptococcal meningitis (n = 14), neurosyphilis (n = 1), mucormycosis (n = 1), cerebral lymphoma (n = 1), and viral encephalitis (n = 10). Definite TBM was diagnosed based on positive Xpert MTB/RIF (n = 34) or ZN microscopy (n = 7) or *Mycobacterium tuberculosis* culture (n = 34). Definite viral encephalitis included 2 cases caused by herpes simplex virus, 2 by varicella-zoster virus, and 6 by cytomegalovirus.

Figure 2 Relative proportion of different diagnoses (including definite diagnoses and probable tuberculous meningitis and toxoplasmosis) according to HIV status



(A) HIV positive patients; (B) HIV negative patients.

Based on neuroradiology and clinical findings, an additional 94 patients were diagnosed with probable TBM (n = 51), brain abscess (n = 8), or probable cerebral toxoplasmosis (n = 35). Based on routine CSF findings and response to treatment, 2 patients were diagnosed with probable bacterial meningitis.

No diagnosis could be made in 53 of 127 HIV-uninfected patients (42%) and 42 of 147 HIV-infected patients (29%) with suspected CNS infection. The relative proportion of different diagnoses (including definite diagnoses and probable TBM and toxoplasmosis) according to HIV status is shown in figure 2, A and B, and table 3. None of 42 HIV-negative patients with clinically suspected acute encephalitis tested positive for arboviruses or enteroviral infection.

Among HIV-uninfected patients with suspected CNS infection, the most common diagnosis was TBM (47%). Among HIV-infected patients, toxoplasmosis was the most common (33%), especially among patients with newly diagnosed HIV, although it was also found in 16 patients with previously diagnosed HIV infection (25%), including 8 patients who had been prescribed cotrimoxazole prophylaxis at some point. Cryptococcal meningitis and viral encephalitis were more common among patients with known HIV infection than among those with newly diagnosed HIV. TBM made up one-fourth of diagnoses in both groups of patients with HIV.

Table 3 Final diagnosis according to HIV status

	HIV-positive (n = 147)	HIV-negative (n = 127)	Total (n = 274)
Tuberculous meningitis	32 (22)	60 (47)	92 (34)
Definite	13	31	
Probable	19	29	
Toxoplasma encephalitis	48 (33)	0	48 (17)
Definite	10	0	
Presumptive	38	0	
Cryptococcal meningitis	13 (9)	1 (1)	14 (5)
Viral encephalitis	7 (5)	3 (2)	10 (4)
Cytomegalovirus	6	0	
Herpes simplex virus	0	2	
Varicella-zoster virus	1	1	
Others	5 (3)	10 (8)	15 (5)
Brain abscess	3	5	
Possible bacterial meningitis	0	2	
Mucormycosis	0	1	
Neurosyphilis	1	0	
Lymphoma	1	0	
NMDAR encephalitis	0	2	
CNS infection of unknown etiology	42 (29)	53 (42)	95 (35)

Diagnoses as defined in table 1. Values are n (%).

Cryptococcal meningitis and viral encephalitis were more common among patients with known HIV infection than among those with newly diagnosed HIV.

Patient treatment and survival

Follow-up was complete during hospitalization, and only 4 cases (3%) were lost during 6 months follow-up. Based on final consensus diagnoses (table 1), patients with TBM (95%) and cryptococcal meningitis (100%) mostly had received appropriate empirical treatment. For patients with a final diagnosis of cerebral toxoplasmosis, 88% had been treated empirically with pyrimethamine–clindamycin. Only 2 of 10 cases with definite viral encephalitis as consensus diagnosis had received empiric antiviral treatment. Patients for whom no final diagnosis could be made (28% of all HIV-infected and 42% of all HIV-uninfected patients) were mostly treated for presumptive tuberculosis (46%), bacterial meningitis (42%), cerebral toxoplasmosis (13%), or viral encephalitis (12%).

Mortality was high: 6 patients (4 HIV-infected and 2 HIV-noninfected) died before any antimicrobial treatment was given. Out of 274 patients, 88 (32%) died during hospitalization, and another 68 (25%) from discharge until 6 months follow-up, resulting in a cumulative mortality of 57% at 6 months. Mortality was strongly associated with HIV infection; 37% of those with HIV and 26% of those without HIV infection died during hospitalization, and 67% of those with HIV and 45% without HIV had died after 6 months follow-up ($p < 0.01$, figure 3). Compared to patients with previously diagnosed HIV infection, those with newly diagnosed HIV had a similar CD4 cell count (median 29/μL vs 30/μL), but a higher mortality (log-rank test 0.03).

Besides HIV, other factors predicting mortality included older age, severity of neurologic presentation, CT and chest X-ray abnormalities, and CSF glucose values (table 4). Among 112 patients who could be interviewed at 6 months, 64% had made a good recovery, 25% had moderate disability, and 11% had severe disability according to the GOS.

Discussion

We conducted a prospective cohort study of patients with suspected CNS infections in a large tertiary referral center in Jakarta, Indonesia. A number of important conclusions could be

drawn. First, patients with CNS infections in this setting present late, commonly with loss of consciousness, motor abnormalities, or other severe clinical manifestations. Second, HIV infection was very common, and very advanced, also among those who had previously been diagnosed with HIV. Third, the most common diagnosis overall was TBM, and among HIV-infected patients it was cerebral toxoplasmosis. In spite of an extensive diagnostic workup, a definite diagnosis could only be made in a minority of patients, Finally, one-third of patients died during hospitalization and almost 60% had died at 6 months, with higher mortality among HIV-infected patients and those with neurologic complications.

Like in many low-resource settings, late presentation and lack of diagnosis lead to poor outcome of CNS infections in Indonesia. Although this study was conducted in the top referral hospital for Indonesia, two-thirds of patients were self-referred, often after considerable delay, with reduced consciousness and with severe neurologic complications. This suggests that patients or doctors in this setting may not appreciate the significance of certain signs and symptoms, or face barriers to timely access to referral. We are planning further studies, including interviews with health practitioners as well as patients and their family, to help design appropriate interventions to reduce late presentation and diagnosis. In addition, routine diagnostic testing for CNS infections in Indonesia is very limited, especially in general or district hospitals. A recent survey among 288 Indonesian neurologists showed that lumbar puncture is often not performed even if CNS infection is suspected, and that standard microbiological testing for CSF is either not available or not covered by public health insurance (Imran, unpublished data, July 27, 2017). Patients may refuse lumbar puncture, as studied in other settings,[13] or doctors may fear complications of a procedure that is infrequently done.

Previous studies in Indonesia have focused on specific CNS infections, like TBM,[14] cerebral toxoplasmosis,[5] or cryptococcal meningitis,[15] but to our knowledge, only one recent study has examined the etiology of CNS infections, and none has used an extensive and systematic clinical, radiologic, and laboratory workup like ours.[6] In the present study, large-volume CSF samples were subjected to a more extensive diagnostic workup, including different diagnostic tests for *M tuberculosis* and several panels for viruses. Nonetheless, no diagnosis could be made in 35% of cases of suspected CNS infection. Other causes may have to be considered including leptospirosis or rickettsial disease, or possibly noninfectious inflammatory disorders such as immune-mediated encephalitis.[16–20] An epidemiologic study of encephalitis in England showed that 42% of

Figure 3 Survival stratified by HIV status

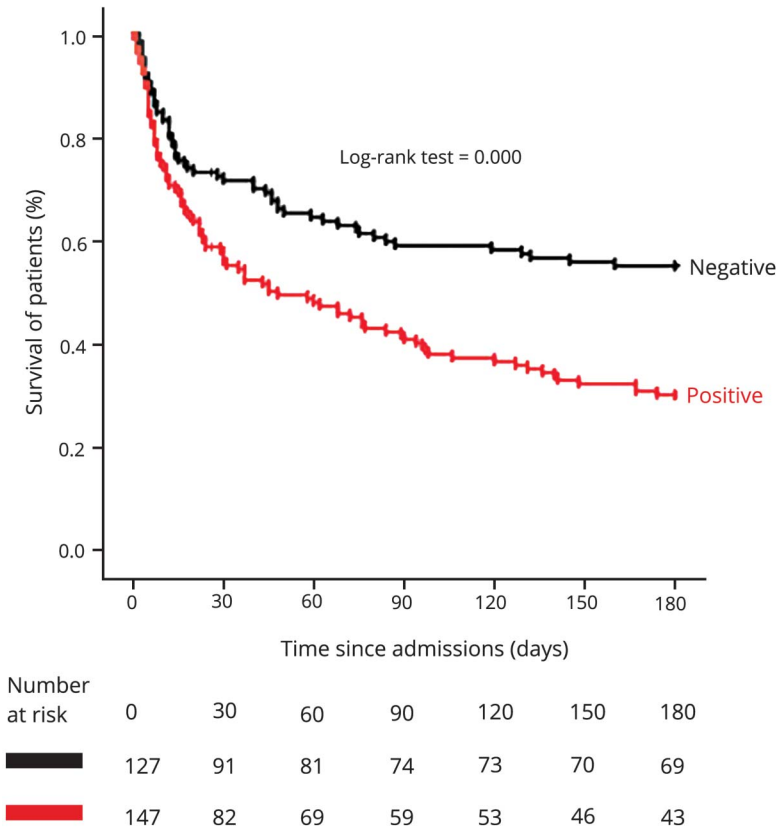


Table 4 Predictors of 6-month mortality according to HIV status

	HIV-positive (n = 147)		HIV-negative (n = 127)		All patients (n = 274)	
	HR	*p*	HR	*p*	HR	*p*
Age, 10-year increase	1.06	0.55	0.28	0.01	0.15	0.03
Glasgow Coma Scale score, 1-point increase	0.86	<0.01	0.87	<0.01	0.88	<0.01
Body temperature, 1° increase	1.34	0.02	1.06	0.71	1.19	0.06
Papilledema	1.45	0.10	1.70	0.05	1.41	0.04
Neck stiffness	1.73	<0.01	2.12	<0.01	1.82	<0.01
CSF:blood glucose ratio, 0.1 increase	0.41	0.21	0.21	<0.01	0.27	<0.01
Chest X-ray abnormality	1.15	0.49	2.38	<0.01	1.45	0.03
CT: brain herniation	2.69	<0.01	0.52	0.37	2.04	<0.01
CT: encephalitis/ cerebritis	1.36	0.18	1.27	0.45	1.50	0.02
Blood neutrophils %, 10% increase	1.25	<0.01	1.13	0.37	1.16	0.03
CD4 cell counts, increase of 10 cells/μL	0.94	<0.01	NA	NA	NA	NA

Abbreviations: GCS = Glasgow Coma Scale; HR = hazard ratio.
HRs were calculated using univariate Cox regression. None of the following predicted mortality: history of seizures or behavioral changes; CSF leucocyte count or protein; infarction, hydrocephalus, abscess, or tuberculoma on CT scan. In multivariate analysis, only papilledema (adjusted HR 1.98, $p = 0.02$) for all patients, herniation on brain CT (adjusted HR 3.64, $p = 0.03$) for HIV-infected patients, and GCS (adjusted HR 0.88, $p = 0.04$) showed a significant association with 6-month mortality.

cases were caused by the infectious agents, 21% caused by autoimmune condition, and 37% of unknown condition.[16] The England study underlines the importance of autoimmune condition as one of the possible causes of encephalitis. However, due to the limitations of the resources, we were only able to perform anti-NMDAR tests in 41 participants, in which we could confirm 2 cases of anti-NMDAR encephalitis. MRI, which is not standard for CNS infections in Indonesia, and novel diagnostic platforms like next-generation sequencing, may help improve diagnosis. However, cohorts of suspected CNS infections from other settings have shown that diagnosis of CNS infections, especially in patients with suspected encephalitis, can be very challenging.[16]

HIV infection proved to be a major factor in our cohort, in terms of both the etiology and outcome of CNS infections. Indonesia has the second fastest growing HIV epidemic in Asia.[2] Although the overall HIV prevalence in Indonesia is low at 0.5%, much higher infection rates are found among specific risk groups, including injecting drug users, men who have sex with men, and sex workers. Out of an estimated 691,000 HIV-infected individuals, only 26% have been diagnosed, and only 9% are currently treated with ART.[2] There are barriers to HIV testing in Indonesia; our recent survey among neurologists showed that for many it was not included in their routine workup of patients with suspected CNS infections (Imran, unpublished data). Our data also showed that although HIV infection often had been diagnosed before, many patients had not yet initiated ART. This underlines the challenges in uptake, retention, and monitoring of ART in Indonesia. HIV viral load is not routinely measured and not covered by government health insurance in Indonesia. The very low CD4 cell counts and the frequent occurrence of toxoplasmosis among ART-experienced patients suggest that many were not adhering to their cotrimoxazole prophylaxis and that many had either stopped taking ART or developed viral resistance. As such, this cohort exemplifies the many challenges in timely diagnosis and adequate treatment of HIV in Indonesia.

As a result of the late and severe presentation and the high proportion of advanced HIV coinfection, outcome was poor. One-third of patients died during hospitalization, and another 25% during 6 months follow-up. A range of different interventions may collectively help improve outcome of CNS infections in low-resource settings, including implementation of state-of-the-art rapid diagnostics, algorithms for rational and timely (empiric) treatment, optimized supportive medical care, intensified antimicrobial treatment (as was shown to be effective for TBM in a clinical trial in Indonesia),[3,21] optimal neuroimaging and ventricular drainage and drainage of abscesses if indicated, and possibly the advent of more effective host strategies. However, earlier recognition, diagnosis, and referral of patients with CNS infections, and improved diagnosis and treatment of HIV as a main risk factor, are likely to improve outcomes or prevent the development of CNS infections.

As this study was performed in the top referral government hospital, caution should be taken when extrapolating the findings to other hospitals and settings in Indonesia. Nonetheless, this cohort study is the largest and most comprehensive study on CNS infections undertaken in Indonesia, providing important data for epidemiology, clinical practice, and further research to improve diagnosis and treatment of CNS infections in Indonesia.

Author contributions

D. Imran: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision, obtaining funding. R. Estiasari: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. K. Maharani: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding. Sucipto: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. D.C. Lestari: drafting/revising the manuscript, acquisition of data. R.E. Yunus: drafting/revising the manuscript, analysis or

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