High mortality in patients with presumed central nervous system (CNS) infections in a tertiary care center in Indonesia

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INTRODUCTION

Central nervous system (CNS) infections are a medical emergency, that needs a proper diagnostic approach and early treatment. Indonesia's tropical climate, biodiversity and populated areas facilitate the transmission of zoonosis and vector borne diseases. Accordingly, a viral etiology, such as Japanese Encephalitis virus, is often considered in case of a presumed CNS infection, as was confirmed in a recent study (1). Furthermore, an increasing number of HIV related deaths result from CNS co-infections (2). Current limited routine diagnostic capacity and low surveillance rates impede a definite diagnosis for the majority of suspected CNS infections in Indonesia. Diagnostics and subsequent treatment of identifiable causes of CNS infections should be a priority. A recent study has elucidated human behavioral factors in this process. Because of hesitancy, lumbar punctures are not routinely performed. According to questionnaires held amongst neurologists this is mostly due to patients that refuse to undergo lumbar punctures because of fear of complications. The study suggests to improve doctors' skills and knowledge (3). Here, we present data from a two year prospective cohort in patients with a suspected CNS infection in East-Java and share similar findings.

METHODS

From April 1st, 2016 to March 30th, 2018 we enrolled patients aged 13 years and above, admitted with fever (≥38ºC) and signs suggestive of a CNS infection to the Department of Neurology in the RSUD Dr. Soetomo hospital in Surabaya, East-Java, Indonesia. This is a regional referral center for Neurology. From all patients or their legal representatives we obtained informed consent. Routine clinical data, blood- and cerebrospinal fluid (CSF) samples were collected. Reports of computed tomographic (CT) scans of the head were evaluated. Lumbar punctures were performed following the normal daily routine. Staining and banal culture were available as routine microbiological assessments, but serological assays were limitedly available due to restrictive financial resources, and polymerase chain reaction (PCR) was not available. Glasgow Outcome Score (GOS) was noted on discharge. Ethical clearance was obtained from the Airlangga University, Faculty of Medicine (ref: 317/Panke.KKE/V/2015). Full criteria are available as Supplementary data 1.

RESULTS AND DISCUSSION

Data was available from 74 out of 89 consented patients (Table 1 and Supplementary data 2). The mean age was 37 years, duration of symptoms 5 days and an altered consciousness was observed in 70% of the cases. CT-scans were available from all patients and we observed abnormalities in up to 60% (see Table 1). In only 47% of cases a lumbar puncture was performed.

Table 1. Characteristics of patients with suspected CNS infections enrolled in the study

		All patients (n=74)
Baseline	Age (yrs)	37 (15-76)
	Male sex n (%)	45 (60.8%)
	HIV-positive	3/74 (4.1%)
	Diabetes Mellitus	5/65 (7.7%)
	Tuberculosis	10/74 (13.5%)
Clinical	Duration of symptoms, median days/n (range)	5/72 (0-180)
	Arthralgia	17/74 (23.0%)
	Chills	17/74 (23.0%)
	Myalgia	18/74 (24.3%)
	Headache	50/74 (67.6%)
	Photophobia	4/74 (5.4%)
	Seizures	22/74 (29.7%)
	Respiratory complaints	27/74 (36.5%)
	Diarrhea	2/66 (3.0%)
	Nausea	14/66 (21.2%)
	Vomiting	17/74 (23.0%)
Examination	High fever (≥39˚C)	7/74 (9.4%)
	Signs of septic shock[a]	0/74 (0%)
	Aphasia	2/74 (2.7%)
	Hemiparesis	14/74 (18.9%)
	Neck stiffness	35/74 (47.3%)
	Glasgow Coma Scale (GCS) median/n, (range)	12/74 (5-15)
	Altered mental status (GCS <14)	52/74 (70.3%)
	Coma (GCS <8)	6/74 (8.1%)
Laboratory investigations	Leukocytosis	48/74 (64.9%)
	Leukopenia	1/74 (1.4%)
	Thrombocytosis	12/74 (16.2%)
	Thrombopenia	4/74 (5.4%)
	Elevated ALT	16/64 (25.0%)
	Elevated AST	14/64 (21.9%)
	CSF evaluated	35/74 (47.3%)
	Polymorph nuclear leukocytes	113/33 (1-898)
	Mononuclear cells	132/34 (0-975)
	Protein	326/35 (1-4400)
	Glucose	48/35 (8-173)
	Ratio glucose/serum	0,4/35 (0.06-1.15)

Table 1. Characteristics of patients with suspected CNS infections enrolled in the study (*continued*)

		All patients (n=74)
Imaging	Chest X-ray performed	42/66 (63.6%)
	No abnormalities	21/42 (50.0%)
	Cardiomegaly	3/42 (7.1%)
	Effusion	4/42 (9.5%)
	Infiltrate	7/42 (16.7%)
	Suspected tuberculosis	7/42 (16.7%)
Neuro-imaging	Brain CT-scan performed	74/74 (100.0%)
	Edema	22/74 (30%)
	Infarction	7/74 (10%)
	Hemorrhage	0/74 (0%)
	Leptomeningeal enhancement	44/74 (60%)
	Hydrocephalus	4/74 (5%)
Outcome	Admitted to	
	Ward	72/74 (97.3)
	ICU	2/74 (2.7)
Discharge outcomes	Duration of hospital stay, mean days/n evaluated (range)	10/68 (1-71)
	survived patients (n=44/68) deceased patients (n=30/68)	15 (1-71) 4 (1-20)
	Death (GOS = 1)	30/74 (40.5%)
	Persistent vegetative state (GOS = 2)	1/74 (1.4%)
	Severe disability (GOS = 3)	1/74 (1.4%)
	Moderate disability (GOS = 4)	3/74 (4.0%)
	Low disability (GOS = 5)	39/74 (52.7%)

Data presented as absolute number/number evaluated (%) and mean (range) unless stated otherwise. HIV: human immunodeficiency virus; ALT: alanine transaminase (ref: <50 U/L); AST: aspartate transaminase (ref: <50 U/L); Leukocyte count ref 3.6-11.0x10^9/L; Thrombocyte count ref 150-400x10^9/L; CSF: cerebrospinal fluid; [a] defined as mean arterial pressure ≤ 65 mmHg.

No data was retrospectively available from the Clinical Microbiology laboratory. All patients received dexamethasone, but antibiotics were administered in only 65%. Fifteen percent of the patients were treated with acyclovir (single or combined with antibiotics). Tuberculostatic drugs were prescribed to 9% of the patients. The HIV prevalence was 4% which seems to transcend the prevalence in the Indonesian population (4), but is low compared to a study that details CNS infections in Indonesia (2).

We found a high in hospital mortality rate of 40%. There are several possible explanations that we noted here. There was a low rate of lumbar punctures with a limited yield of determination of causative organisms or viruses. This hinders an overview of treatable causes of CNS infections. Furthermore, all patients received adjunctive dexamethasone treatment, which is discouraged in

resource-limited settings (5). HIV and co-infections might possibly be underdiagnosed, which may have led to inadequate drug prescription patterns.

This underlines the need for an integrative approach. We suggest that the number of lumbar punctures in presumed CNS infections needs to increase drastically, to guarantee sufficient numbers as to identify cases that benefit from accurate treatment. Outcomes of diagnostic testing would then direct treatment choices. A minimal set of routine assays should be available for blood and CSF. This needs to be established in-hospital, without being subjected to financial barriers such as insurance or reimbursement. This preferably includes molecular diagnostics for bacteria, Herpes Simplex virus-1, HIV and tuberculosis (6). A random selection of samples may be sent out for reference purposes. We acknowledge the suggestion of encouraging the neurologists to put effort in convincing the patients of the importance and the safety of a lumbar puncture, while also taking into account their own knowledge and skills gaps (3).The capacity to treat, study and ultimately prevent CNS infections in Indonesia needs urgent attention. International collaboration between reference laboratories, necessary to validate and improve the diagnostics, is crucial, but may be hampered due to laws restricting data exchange (7).

Supplementary data 1:

Meningitis was defined as fever, accompanied with at least one of the following: headache and signs of meningeal irritation. Encephalitis was defined as fever, accompanied with at least one of the following: a change in mental status, focal neurological symptoms or seizures. Patients that initially presented with fever (≥38ºC) documented at the Emergency Department and fulfilling the case definitions for meningitis or encephalitis were also eligible for participation, whereas those referred from another hospital were not eligible for participation. Standardized case report forms (CRF) and the OpenClinica clinical data management system (version 3.12), were used to collect: demographic characteristics, medical history, symptoms and signs on admission and routine lab parameters. All patients were requested to undergo a diagnostic lumbar punction as part of routine work-up, in case there were no relevant contra-indications. Patients were treated and followed-up to routine, this included dexamethasone treatment for all meningitis and encephalitis cases, complemented with antibiotic, antiviral or anti tuberculous medication. Clinical samples, including CSF were taken based on the clinicians discretion, and subsequent analysis was performed per local practice. Discharge or in-hospital decease was considered as study exit. From study exit patients, the Glasgow Outcome Score (GOS) was noted, and for survivors we noted the discharge destination. No sample size calculation was performed. Descriptive analysis is used to display the data, displayed with the use of IBM SPSS Statistics version 25 (SPSS Inc). Missing data is shown in numbers analysed versus numbers in the cohort. Ethical clearance for this study was obtained from the ethical review board of the Airlangga University, Faculty of Medicine acting on behalf of the Board of Directors of the RSUD Dr. Soetomo hospital (ref: 317/Panke.KKE/V/2015).

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