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ORIGINAL ARTICLE

Different presentations and outcomes between HIV-infected and HIV-uninfected patients with Cryptococcal meningitis

Chia-Hung Liao [a,b], Chih-Yu Chi [a], Yi-Jen Wang [a], Shu-Wen Tseng [a], Chia-Huei Chou [a], Cheng-Mao Ho [a], Po-Chang Lin [a], Mao-Wang Ho [a,*], Jen-Hsian Wang [a,c]

[a] *Section of Infectious Diseases, Department of Internal Medicine, China Medical University Hospital, Taichung City, Taiwan*
[b] *Department of Internal Medicine, Fong-Yuan Hospital, Department of Health Executive Yuan, Taiwan*
[c] *China Medical University, Taichung City, Taiwan*

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Background and Purpose: Cryptococcus species are the most common causative agents of fungal meningitis. Different populations may show different clinical manifestations and outcomes. In this retrospective study, we investigated these differences in patients with and without HIV infection.
Methods: From 1995 to 2009, we collected data from HIV-infected or HIV-uninfected patients aged 18 years or over who had cryptococcal meningitis (CM) in a medical center in Taiwan. We reviewed and analyzed their demographic data, clinical manifestations, therapeutic strategies and outcomes.
Results: Among the 72 patients with CM, 19 HIV-infected patients were predominantly younger males, and all of them had AIDS status when CM was diagnosed. In contrast, the 53 HIV-uninfected patients were mostly older males with underlying diseases. The time from initial symptoms to diagnosis was shorter in HIV-infected patients (median 10 vs. 18 days, $p = 0.048$). The HIV-infected patients presented with less pleocytosis ($p = 0.003$) and lower protein levels in the cerebrospinal fluid (CSF), but a higher proportion had positive results for cryptococci in the CSF (90% vs. 60%, $p = 0.02$) and blood (53% vs. 21%, $p = 0.009$) cultures. Surgical drains and repeated lumbar punctures for the management of increased intracranial pressure were performed in 47% of the HIV-infected patients and 38% of the HIV-uninfected patients. A lower mortality rate was observed in the HIV-infected patients ($p = 0.038$). On

* Corresponding author. Section of Infectious Diseases, Department of Internal Medicine, China Medical University Hospital, Number 2 Yuh-Der Road, North District, Taichung City 40447, Taiwan.
E-mail address: Liaoch0809@gmail.com (M.-W. Ho).

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multivariate analysis, initial CD4 count $\leq 20/mm^3$ was an indicator of death or relapse in HIV-infected patients. In the HIV-uninfected group, the initial high cryptococcal antigen titer in the CSF ($\geq$1:512) and hydrocephalus were related to unsatisfactory outcomes.
Conclusion: In addition to well-known differences, we found a lower mortality in HIV-infected patients than in HIV-uninfected patients. Cryptococci and inflammation in the central nervous system may play important roles in the pathogenesis of CM. Low intensity of inflammation and effective surgical CSF drains for increased intracranial pressure and cryptococci removal may contribute to lower mortality in HIV-infected patients.

Introduction

Cryptococci are environmental fungi that can cause infectious diseases in humans. *Cryptococcus neoformans* and *Cryptococcus gattii* are the most common pathogenic species across the worldwide and can be classified into five serotypes.[1,2] Risk factors for cryptococcal infections, including infection with HIV, liver cirrhosis, diabetes mellitus, solid organ transplantation, malignancies, rheumatologic diseases, corticosteroid use and chronic kidney disease, are well-documented.[2,3] Occasionally, these pathogens also infect immunocompetent patients.[4]

The central nervous system (CNS) is a common site for cryptococcal infection. Cryptococcal meningitis (CM) is one of the most common opportunistic infections in HIV-infected patients.[5,6] Similarly, the pathogen can also infect HIV-uninfected patients causing severe meningitis.[4] This type of infection causes high mortality rates in HIV-infected (9%—55%) and HIV-uninfected patients (15%—44%), even with appropriate treatment.[4,6—8] Therefore, the diagnosis and treatment of CM remains challenging for clinicians.

Different clinical presentations of CM in HIV-infected and HIV-uninfected patients have been described.[4,5,7] Some researchers have compared mortality the rates of HIV-infected and HIV-uninfected patients,[8—12] but the results have been inconsistent and this prompted us to investigate this controversial issue.

Methods

Patients and definitions

From 1995 to 2009 we conducted a retrospective study at China Medical University Hospital (CMUH, 2000 beds in mid-Taiwan), a tertiary hospital. We enrolled all CM patients aged 18 years or over. CM was defined as isolation of *Cryptococcus* species from cerebrospinal fluid (CSF) culture, positive CSF India ink or positive CSF cryptococcal antigen (CrAg) titer, and consistent clinical features of meningitis. The diagnosis and classification of HIV infection, AIDS status and opportunistic infection/malignancy were performed on the basis of the standard criteria proposed by the US Centers for Disease Control and Prevention in 1993.[13] Predisposing factors of CM were identified in all of our patients.[2,3] Corticosteroid use encompassed that those who could not withdraw from corticosteroids or those who required at least prednisolone 20 mg daily. The Charlson comorbidity score was used to evaluate comorbidity status. The time from the initial symptoms to the time of definite diagnosis was considered the symptom duration.[11]

Clinical symptoms and all laboratory data were recorded on presentation to our hospital. For treatment classification, the patients who received initial antifungal therapy for at least 7 days were divided into different groups (amphotericin B dosage: 0.5—1.0 mg/kg daily; fluconazole dosage: 400—800 mg daily; flucytosine dosage: 100 mg/kg daily; lipid amphotericin B dosage 3—5 mg/kg daily). Flucytosine and lipid amphotericin B had been available since 2007.[14,15] Repeated lumbar punctures and temporary drains like Ommaya reservoirs, lumbar drains or external ventricular drains for increased intracranial pressure (IICP) control were also analyzed. Permanent shunts for long-term CSF drainage were collected separately.

All patients were followed up until death or for at least 6 months after discontinuation of antifungal therapy. Outcomes[4,16] were categorized as:

- cure/success: a drug-free interval >1 year, and no reappearance of symptoms;
- improved: the same definition for cure/success but the last follow-up examination or death occurred within a year;
- fail: death due to first treated CM;
- relapse: defined as for improved, but with reappearance of symptoms with CSF culture/India ink proof after therapy had been stopped; and
- indeterminate: death due to causes other than CM, and the treatment course was incomplete.

The outcomes were further classified as satisfactory (cure/success or improved) and unsatisfactory (death, relapse or indeterminate).[4] Patients in the satisfactory group were evaluated further for sequelae.

Laboratory methods

In cases of CM, an initial lumbar puncture was performed in each patient and open pressure was recorded. CSF and blood samples were collected for complete blood cell counts and differential counts, glucose, protein, culture and CrAg tests; a CSF staining with India ink was also