



Cryptococcus Neoformans Meningitis Cases Among China's HIV-Infected Population may have been Severely Under-Reported

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Received: 28 May 2020 / Accepted: 18 September 2020 / Published online: 28 September 2020
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Abstract Cryptococcal meningitis (CM) is the leading fungal infection of the central nervous system. Globally, most CM cases have been reported from patients with compromised immunities, especially those infected with HIV. However, reports from China have shown that most CM infections were from HIV-negative, immunocompetent hosts. Here, we reviewed the published reports and found those studies were almost exclusively based on patients from hospitals associated with Chinese universities but not from specialized infectious diseases hospitals where most Chinese HIV-infected patients have been treated. Thus, we believe CM cases among China's HIV-infected population may have been severely under-reported. Analyses of CM cases in specialized

infectious diseases hospitals are needed to identify the true epidemiological pattern of CM in China.

Keywords Cryptococcal meningitis · HIV · Epidemiology · China

Cryptococcal meningitis (CM) is a lethal fungal infection mainly caused by two closely related basidiomycete yeasts in the genus *Cryptococcus*: *Cryptococcus neoformans* and *Cryptococcus gattii* [1]. Epidemiological studies have shown that *C. neoformans* causes over 80% of global CM cases each year, with the majority of cases in immunocompromised individuals, such as HIV-infected patients [2]. In contrast, *C. gattii* seems to mainly infect apparently immunocompetent hosts [3].

Beginning in the 1970s, cryptococcosis started to attract significant medical attention due to its increasingly frequent associations with hosts with impaired cell-mediated immunity, such as malignancy or organ transplantation [1, 4]. Because of the HIV pandemic, CM became a significant HIV-associated infection since the 1980s, and the number of cases increased rapidly, especially in Sub-Saharan Africa, where more than 90% of CM cases occurred in HIV-infected individuals [5, 6]. In 2014, it was estimated that globally, about 223,000 cases of CM were associated with HIV, and most of which were caused by *C. neoformans* [7]. Consequently, CM has been defined

Handling Editor: Cunwei Cao.

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Table 1 Studies describing the epidemiology of cryptococcal meningitis from China

Data source	CM in HIV-positive patients	CM in apparently immunocompetent hosts	Reference
University hospitals in 15 provinces	7.5% (9/120)	70% (84/120)	[9]
14 University hospitals in four broad geographic regions	4.1% (4/104)	No data	[10]
Huashan Hospital of Fudan University, Shanghai	8.4% (13/154)	66.9% (103/154)	[11]
Changzheng Hospital of Second Military Medical University, Shanghai	24.6% (16/61)	71.1% (32/45)	[12]
Peking s, Beijing	10.3% (7/68)	19.1% (13/68)	[13]
West China Hospital of Sichuan University, Sichuan province	37.6% (32/85)	50.9% (27/53)	[14]
Affiliated Hospitals of Nanchang University, Jiangxi province	40.7% (35/86)	11.6% (10/86)	[15]
Systematic review of published cases across China	16% (1403/8769)	17% (1490/8769)	[16]

as an opportunistic fungal infection because it mainly occurs in immunocompromised populations, particularly HIV-infected individuals.

In China, CM is mainly caused by *C. neoformans*, with the majority of the strains (> 90%) belonging to a specific multilocus sequence type ST5 [8]. However, different from those reported in other countries, several studies from China indicated that an extremely high proportion (approximately 85%) of CM cases were found in HIV-uninfected patients, including mostly immunocompetent hosts (Table 1) [9–16], with the HIV-infected patient population (16%) being significantly lower than in most countries and regions such as the United States (80%), Brazil (95%) and Europe (77%) (Fig. 1) [17–19]. These results have led to the conclusion that the epidemiological pattern of CM in Mainland China is different from those in other regions [20]. If true, the results would suggest that immunocompetent Mainland Chinese might be more susceptible than people in other regions to *C. neoformans* infections, especially to *C. neoformans* strains of the ST5 genotype [21].

However, outside of Mainland China, there has been no report of healthy ethnic Chinese having a higher proportion of CM cases than immunocompromised ethnic Chinese. We speculate that the reported differences in epidemiological patterns of CM between Mainland China and other regions were likely due to biased reporting in China. In China, the government has strict policies and regulations for the diagnosis and treatment of patients with severe infectious diseases. Almost every Chinese municipality has a specialized hospital or a public health center dedicated for treating patients with severe infections. These specialized hospitals typically take on patients

from other hospitals or community clinics who are suspected to have contracted a highly infectious and virulent pathogen, such as HIV and tuberculosis. Notably, all the previously reported surveys of CM in China were from teaching hospitals associated with universities where HIV-infected patients are typically not admitted for treatment (Table 1), and none of the published studies on CM in China has come from the specialized infectious disease hospitals. Thus, CM patients, if they were first diagnosed with HIV and treated at the infectious diseases hospitals, have most likely not been reported in the studies.

It is estimated that there are about 5000–10,000 cases of CM among HIV-infected patients in China annually [7]. According to a recent meta-analysis of cryptococcosis in China that included 8769 cases, only 17% of the cases were found to be immunocompetent [16, 20], a rate similar to those in most other countries and regions. Thus, we believe that the low proportion of Chinese CM cases reported from HIV-infected patients was due to under or no reporting for data from this group of patients. Our argument above for the reported low prevalence of CM cases in HIV-infected patients in China is further supported by the observation of another important human fungal pathogen, *Talaromyces marneffei*. *Talaromyces marneffei* is endemic to Southern China (specially in Guangxi) and Southeast Asia. In both China and Southeast Asia, most reported cases of infection by this fungus have been found in HIV-infected patients [22]. Our analyses of the literature revealed that the reports on *T. marneffei* from China have involved both university-affiliated hospitals and specialized infectious diseases hospitals [22 and references therein].

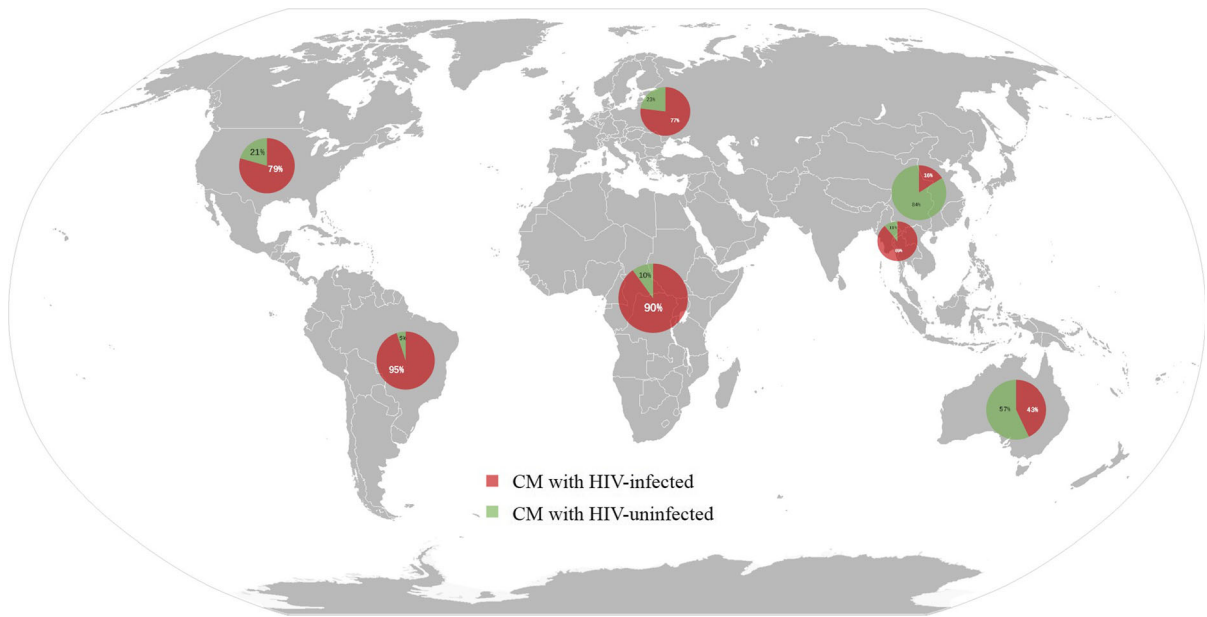


Fig. 1 The proportion of CM among HIV-infected populations in the published literatures in major representative countries and regions [16–19]

The actual relationship between HIV status and the incidence of CM should be thoroughly investigated by clinicians and epidemiologists from not only university hospitals who have published most of the cases so far, but also from infectious diseases hospitals who have been treating most of China's HIV-infected patients. Specifically, we would like to suggest that infectious disease physicians with expertise on CM in university-affiliated hospitals in China reach out to and collaborate with physicians working in specialized infectious diseases hospitals (and all other hospitals) to increase the overall capacity for CM diagnosis and to obtain accurate epidemiological data about CM (and other infectious diseases) in China.

In conclusion, the reported difference between China and elsewhere in the relative proportions of CM in HIV-infected patients and apparently immunocompetent hosts is likely not a true representation of the actual epidemiology of CM. In China, many of the CM cases in HIV-infected patients at the specialized infectious diseases hospitals have not been reported in the published studies. Clinicians at all hospitals in China should remain alert to diagnose this fatal mycosis in HIV-infected patients as well as other infectious diseases, and share data in peer-reviewed

publications. As we can see during the last few months dealing with the COVID-19 pandemic, data sharing is essential to guide research and the decision-making for public health agencies to develop appropriate measures to control infections.

Acknowledgements This work was supported by the National Natural Science Foundation of China (Grant No. 81201269).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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