Author’s response to reviews

Title: The clinical characteristics and therapeutic outcomes of cryptococcal meningitis in elderly patients: a hospital-based study

Authors:

Wen-Neng Chang (cwenneng@ms19.hinet.net)
Wan-Chen Tsai (u8901048@cgmh.org.tw)
Chia-Yi Lien (U9301024@cgmh.org.tw)
Jun-Jun Lee (Claire17@cgmh.org.tw)
Wen-Chiu Hsiao (switzerland1107@gmail.com)
Chi-Ren Huang (suika68@cgmh.org.tw)
Nai-Wen Tsai (naiwen@adm.cgmh.org.tw)
Chiung-Chih Chang (neuro099@adm.cgmh.org.tw)
Cheng-Hsien Lu (chlu99@ms44.url.com.tw)

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We thank the reviewers for their comments and suggestions. We have revised the manuscript accordingly and the changed areas are marked.

Reviewer 1

Minor concern: In the discussion part, the aspect of a foreseeable bias between the "non-elderly" and "the elderly" should be more discussed. What is the factor which causes the finding, the age itself or other factors?

We have added the following in the Background section, and added a new reference (reference 1):

Aging is a complex process that negatively impacts the development of the immune system and its ability to function. In addition, concomitant disabilities and comorbidities are common in the elderly. These factors render elderly individuals more vulnerable to infectious diseases.
What is the significance of Indian ink and cryptococcal cryptococcal AG Ag titer (≥1:1024). This should be described more in detail.

Because of the large polysaccharide capsule, C. neoformans can be visualized by India ink staining. Organisms that possess a polysaccharide capsule exhibit a halo around the cell against the black background created by the India ink. The higher the fungal burden, the higher the positive rate.

A cryptococcal Ag titer ≥ 1:1024 is an important cut-off point for the prognosis of CM and has been used in many studies of CM, including one of our previous reports (reference 11).

Neither a positive India ink stain nor cryptococcal Ag titer ≥ 1:1024 were significant factors; therefore, we only added some statements in the Methods section to denote their clinical significance.

Regarding the neuroradiological findings a typical MRI would be interesting.

Thanks for your suggestion. We have added a new figure (Figure 2) to demonstrate the main MRI findings.

Reviewer 2

Introduction section

As a general comment, the authors have to discuss the commonest forms of meningitis in elderly (i.e. Listeria and pneumococcal meningitis) suggesting how they can differentiate these forms from CM (see Listeria monocytogenes meningitis in the elderly: Distinctive characteristics of the clinical and laboratory presentation. J Infect. 2015 Jul;71(1):134-6. and Listeria monocytogenes meningitis in the elderly: epidemiological, clinical and therapeutic findings. Infez Med. 2016; 24:105-11). Are there reasons to suspect CM in particular areas? Line 5 there is no need to add (C.) after Cryptococcus Line 9 'population aging', not aging population

Thank you for this important suggestion. We have reported serial studies of bacterial meningitis in adults including those in elderly patients since 1986 (see reference 20). Compared with the findings of adult bacterial meningitis (ABM) reported in Western countries, our serial studies have shown great epidemiologic differences in the underlying conditions and implicated pathogens. In Taiwan, the most commonly implicated bacterial pathogen of ABM is K. pneumoniae, and K. Pneumoniae ABM is most commonly found in patients with DM and cirrhosis as the underlying conditions. In our serial studies of ABM, L. monocytogenes was not a common bacterial pathogen in ABM including the elderly (see references 5 and 20). Therefore, in the revised manuscript, we have added a related statement and short discussion in the Background and Discussion sections.
In the Background section:

“Clinically, in contrast to acute bacterial meningitis, patients with CM, which classified as chronic meningitis, have a slower onset of symptoms, evolving over days to a few weeks [10]. Nevertheless, laboratory studies such as the measurement of cryptococcal antigen titer and/or culture of C. neoformans are still the mainstay for a definite diagnosis. In our previous study of the clinical characteristics of bacterial meningitis in elderly patients [5], the clinical presentations were similar to those of non-elderly adults.”

In the Discussion section:

“In the current study, headache, fever and altered consciousness were the main clinical presentations of the 38 elderly patients with CM. These clinical presentations were similar to those of the non-elderly adults with CM (Table 1), and to both elderly and non-elderly adults with acute bacterial meningitis [5, 20]. Therefore, it is difficult to differentiate the exact type of meningitis if only the clinical presentations are considered. To avoid a missed or delayed diagnosis of CM in the elderly, keeping this specific infectious syndrome in mind and conducting appropriate studies for CNS infections are needed, especially in elderly patients with altered consciousness and/or headache and/or fever.”

Methods The sample is too small to perform an accurate multivariate analysis

We agree that the sample size is not large and the number of variables considered for the multivariate logistic regression analysis is small. Therefore, in the revised edition, only the variables with a p-value < 0.01 were further analyzed using multivariate logistic regression analysis. Based on the stepwise procedures, only three variables were selected as important variables predicting the outcomes. Thus, the maximum likelihood estimates of the coefficients are valid in the analysis.

To address the limitation of the small sample size defect, we have added the statement:

“This study is limited by the small number of patients, and further large-scale studies are needed to better delineate this specific infectious syndrome.” in the Abstract and Conclusion sections.

Results

The authors have to report the percentage of patients with risk factors for immunocompromission in both groups (is immunosenesence a risk factor for CM?) and compare this finding between the groups.
The epidemiologic trend of CM in Taiwan is somewhat different from that of other regions. From the results of studies of CM in Taiwan (including our several previous study results), we know that most adults with CM are not HIV-positive.

It is a good suggestion to classify the patients into those with or without an immune-compromised state for comparison. In the revised edition, we have classified the patients into those with or without an immune-compromised state according to the criteria reported by Rubin et al (Reference 13). In Table 1, the presence or lack of an immune-compromised state was of no statistical significance.

In the Methods section, we have added the following statement:

“Because immune condition is an important factor in the underlying condition of CM patients, we also classified the 99 enrolled adult CM patients into those with and without an immune-compromised state [13] for comparison.”

Are there differences related to treatment schedules? It is not clear which population (I assume aging Vs not aging) is considered for multivariate analysis.

In our hospital, we followed the therapeutic guidelines for CM meningitis (references 8 and 12) and modified the therapeutic regimen of each patient according to their physical and medical conditions including body weight and concomitant medical conditions. Therefore, there was no much difference in treatment schedule.

In the revised edition, we have modified the statement of patient management to: “During the study period, the main antifungal regimen was amphotericin B +/- flucytosine +/- fluconazole for induction, consolidation and maintenance therapy.”

How the authors assess ’recent cerebral infarction? Elderly patients can have vascular lesions that are not attributable to CM

It is true that elderly patients can have vascular lesions that are not attributable to CM. Using MRI criteria of acute/subacute cerebral infarction, we have reported several related papers (see references 8, 24, 26) dealing with cerebral infarction in CM patients. In this study, 14 enrolled CM patients were found to have recent cerebral infarction. Among these 14 patients, recent cerebral infarction was diagnosed using MRI criteria in 13 patients. The recent cerebral infarction in the other patient was diagnosed by CT findings (a 32-year-old man, AIDS (+), acute diplopia and right lower leg weakness, brain CT: ill-defined low densities at left midbrain and pons).

Discussion
The authors have to underline in this section which are the characteristics to be considered to suspect a so uncommon infection in the aging population.

We agree that this is a very important issue for this topic. However, as we stated in the Background section “…. the classic presentations of infectious diseases are not always noted in elderly patients, making it difficult to make a diagnosis leading to a delay in treatment.”

To address this issue, we have added a short statement in the Discussion section:

“In the current study, headache, fever and altered consciousness were the main clinical presentations of the 38 elderly patients with CM. These clinical presentations were similar to those of the non-elderly adults with CM (Table 1), and to both elderly and non-elderly adults with acute bacterial meningitis [5, 20]. Therefore, it is difficult to differentiate the exact type of meningitis if only the clinical presentations are considered. To avoid a missed or delayed diagnosis of CM in the elderly, keeping this specific infectious syndrome in mind and conducting appropriate studies for CNS infections are needed, especially in elderly patients with altered consciousness and/or headache and/or fever.”

As reported in the results section, the relationship between vascular lesions and CM is intriguing, but it needs an accurate literature analysis in the aging population that was not performed in this section.

After a thorough search of PubMed, we could not find a specific topic on cerebral hemodynamics and/or cerebral infarction in elderly CM patients. It is known that CM may cause vasculitis, especially involving the small vessels around the skull base. In 2007, 2011 and 2018 (references 8, 24, 26), we reported results using MRI-based examinations to evaluate the cerebral hemodynamics and acute/subacute cerebral infarct (ASCI) in CM meningitis. In these studies, we found that: 1) changes in cerebral hemodynamic may occur in the early stage of CM and may last for the duration of CM treatment; 2) around 20% of HIV-negative adults with CM may have ASCI, and that the presence of DM and old age were significant factors for the development of ASCI in HIV-negative adults with CM; 3) the presence of basal meningeal enhancement was an important MRI finding for the development of ASCI, which may indicate that in CM, the basal meninges are the location of most severe inflammation, and this may affect the adjacent small vessels with the subsequent development of ASCI. Therefore, we have added a short discussion of this issue in the revised edition as follows:

“With the increasing size of the elderly population and evolving neuroimaging technology, silent cerebral infarction has garnered a lot of attention [25]. The prevalence of cerebral infarction in the elderly population is known to increase steadily with age, and well-known cardiovascular risk factors and the metabolic syndrome are also important risk factors for the development of cerebral infarction in the elderly [25]. Our previous study revealed that old age was a significant factor for the development of cerebral infarction in CM patients [26]. In addition to age, many other factors may also play a role in the disturbance of cerebral hemodynamics and the subsequent development of cerebral infarction in patients with CM [24, 26], in which obvious basal meningeal enhancement as shown in brain MRI may play a significant role [8, 24, 26]. Increased basal meningeal enhancement is an important finding in brain MRI and confirms that
inflammatory reactions are most intense in the basal meninges of patients with CM [8, 24, 26], and that local lenticulostriate and thalamoperforating arterioles are affected by such inflammatory processes with the subsequent development of cerebral infarction.”