Prediction of Hospital Discharge Outcome From Changes in Albumin Quotient and Cerebrospinal Fluid Lactate Dehydrogenase in Patients With Cryptococcal Meningitis

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Abstract

Background

Cryptococcal meningitis (CM) is a life-threatening infection of the central nervous system that occurs in healthy individuals and immunocompromised patients, and reliable prognostic parameters are needed urgently. This study analyzed the clinical characteristics and laboratory findings of CM patients from two tertiary care hospitals in China between 2015 and 2019, aiming to provide reliable prognostic factors for patients with CM.

Methods

Clinical characteristics and laboratory findings of CM patients were retrospectively reviewed. The unfavorable outcome was defined as no improvement or worsening symptoms and signs or persistent positive results for CSF culture or death after starting treatment. The significant differences in clinical characteristics and symptoms between the patients with favorable and unfavorable outcomes were descriptively analyzed. For comparison of mean values of laboratory results between the patients with favorable and unfavorable outcomes, the *t* test was performed.

Results

63 patients with CM were enrolled in this study and 67% were men. 38/63 patients were confirmed to be HIV serology positive. The mean onset age of all patients was 49 ± 15 (20–77) years. For clinical characteristics, headache, nausea and/or vomiting, and fever were the most common symptoms. Older age and disturbance of consciousness tended to poor prognosis. Changes in serum antioxidant parameters were significantly associated with clinical outcome. For CSF parameters, there were significant correlations between changes in leukocyte count, lactate dehydrogenase and chloride, and outcomes in different groups. For HIV-infected patients, increased CD4⁺ T cell counts suggested good prognosis. Increased CSF/serum albumin quotient (Qalb) was indicative of unfavorable outcome in HIV-negative patients.

Conclusions

In summary, CSF lactate dehydrogenase and albumin quotient may improve prediction of outcome in patients with CM. We recommend incorporation of Qalb value analysis and pay attention to change of CSF LDH during hospitalization.

Background

Cryptococcal meningitis (CM) is an invasive infection of the central nervous system (CNS) caused by *Cryptococcus neoformans* and *Cryptococcus gattii* complexes, and occurs in healthy individuals and immunocompromised patients [1, 2]. *Cryptococcus* yeasts are ubiquitous and usually acquired by inhalation. The initially germinate in the host lungs and then disseminate to other organs, most notably

the CNS, which is responsible for CM [3]. Despite appropriate antifungal treatment, the management of CM remains challenging [4]. The global burden of CM is nearly 250,000 cases annually, with mortality rates of 100% if untreated [5]. Thus, further reliable strategies for improving the overall outcome are urgently needed.

In the human brain, albumin is responsible for about half the total antioxidant capacity and may exert beneficial or harmful effects during meningitis [6, 7]. Cerebrospinal fluid (CSF)/serum albumin quotient (Qalb) is generally considered to be the best indicator of CSF barrier dysfunction for blood-derived proteins [8]. High Qalb has a beneficial effect on disease progression in patients with tuberculous meningitis [9]. However, in patients with CM, decreased Qalb is related to clinical improvement [10]. The specific values of Qalb in patients with and without HIV infection are unknown. HIV-infected patients with CM differ from their HIV-negative counterparts in that they have little inflammatory response in the CSF, large fungal burdens, and few mass lesions [11]. More CM patients without HIV infection have increased Qalb compared with CM patients with HIV infection [12, 13]. Lactate dehydrogenase (LDH) is widely distributed in body tissues such as heart, brain and muscle. It contains five isoenzymes and is a critical enzyme in glycolysis [14]. Previous studies revealed the clinical implications, including auxiliary diagnosis and prognostic significance, of CSF LDH and its isoenzymes in various neurological diseases, including cerebral infarction, CNS infections and brain tumors [15–19]. However, those studies mainly focused on comparison of different diseases, and none involved HIV-infected patients. Therefore, we conducted a retrospective study and evaluated the prognostic values of Qalb and CSF LDH in CM patients with or without HIV infection.

Methods

Study setting and patients

We retrospectively reviewed the medical records of patients with CM admitted to the Nanning Fourth People's Hospital and Shanghai Changzheng Hospital between January 2015 and December 2019. We enrolled 38 HIV-positive and 25 HIV-negative patients with CM. The inclusion criteria were: (1) confirmed CM diagnosis; and (2) availability of follow-up data. Patients were excluded for the following reasons: (1) antifungal treatment prior to admission; (2) recurrent CM; (3) age < 18 years; and (4) incomplete medical records. The diagnosis of CM was based on positive CSF tests, including isolation of *C. neoformans* in CSF culture; positive CSF cryptococcal antigen test (IMMY, Norman, OK, USA); positive CSF India ink staining; and clinical features of meningitis [20]. All of the enrolled CM patients were treated with amphotericin B-containing regimen according to the 2010 guidelines of Infectious Diseases Society of America and World Health Organization [20]. Patients were divided into HIV-positive and HIV-negative groups, which were further divided into favorable and unfavorable outcome groups according to the outcome on discharge.

Data collection and definitions

For each patient, the following data were collected: age, sex, duration of symptoms before admission, underlying diseases, antifungal regimen, clinical manifestations, and laboratory findings including serum and CSF parameters. Discharge data were used to determine the outcome. Favorable outcome was defined as: (1) stable condition, and resolution or improvement of symptoms and signs compared with those at admission; and (2) clearance of pathogen from CSF. Unfavorable outcome was defined as: (1) no improvement or worsening symptoms and signs compared with those at admission; (2) persistent positive results for CSF culture; or (3) death during hospitalization [21].

We divided the laboratory examination data collected from patients into two groups, namely favorable outcome group and unfavorable outcome group. Further, each group contains two sets of data, namely before treatment and after treatment. P1 and P2 indicate the comparison between before treatment and after treatment of favorable outcome group and unfavorable outcome group. We compared before treatment data between favorable outcome group and unfavorable outcome group in order to explore whether the two groups were at the same baseline before treatment, P3 indicates the statistical result. Similarly, we compared after treatment data between favorable outcome group and unfavorable outcome group in order to explore whether there were differences between the two groups after treatment, P4 indicates the statistical result.

Statistical analysis

SPSS version 23 (IBM, New York, NY, USA) was used for statistical analysis, and the categorical data were reported as means $\pm$ standard deviations or percentages. For comparison of mean values between two independent groups, the two-tailed, unpaired two-sided *t* test or Mann–Whitney *U* test was performed. For comparison of mean values between two paired groups, the two-tailed paired *t* test was performed. For comparison of categorical data, the chi-square test or Fisher's exact test was performed. $P < 0.05$ was considered statistically significant.

Results

Patients' characteristics on admission

We included 63 patients (42 male and 21 female) with CM. Demographics and clinical characteristics are shown in Table 1. The mean onset age of all patients was 49 ± 15 (20– 77) years. The average age of HIV-positive patients was significantly younger than that of HIV-negative patients ($P < 0.001$). Compared with HIV-negative patients, the onset age of HIV-positive patients was 30– 60 years ($P = 0.0073$), compared with > 60 years in HIV-negative patients ($P = 0.0004$). There were no significant differences in duration of symptoms before admission ($P = 0.1506$) and sex ($P = 0.4194$) between HIV-positive and HIV-negative patients. HIV-positive patients tended to have acute onset (≤ 2 weeks, $P = 0.0017$) and HIV-negative patients tended to have chronic onset (> 4 weeks, $P = 0.0243$). Most of the enrolled patients (38/63) had positive HIV serology, but only four received antiretroviral therapy before admission. Headache (87.3%), nausea and/or vomiting (60.3%), and fever (57.1%) were the most common

symptoms. We defined eight underlying diseases. Tuberculosis-related diseases (including pulmonary tuberculosis and tuberculous meningitis) were the most common (34.9%), followed by hypertension (19.0%), especially in the HIV-negative patients ($P = 0.0001$). All patients immediately received amphotericin-B-containing regimens after diagnosis. Flucytosine and fluconazole were also used for routine antifungal treatment. Fluconazole was used more for HIV-infected patients ($P = 0.0172$) because they often had concomitant oral fungal infections before diagnosis with CM [22, 23].

Characteristics of HIV-positive and HIV-negative patients

Clinical characteristics are shown in Table 2. There were 38 HIV-positive patients and 20 (52.6%) had a favorable outcome on discharge. The mean onset age was 43 ± 13 (23–76) years and 27 (71.1%) were men. There were no significant differences in terms of age ($P = 0.2322$), sex ($P = 1.0000$), duration of symptoms before admission ($P = 0.1022$), symptoms include fever ($P = 0.7449$), disturbance of consciousness ($P = 0.0967$), headache ($P = 0.6630$), nausea and/or vomiting ($P = 1.0000$) and seizures ($P = 0.0828$) and underlying diseases include hypertension ($P = 0.4737$), diabetes ($P = 1.0000$), tuberculosis-related disease ($P = 1.0000$), liver disease ($P = 1.0000$), renal disease ($P = 0.4879$) and autoimmune disease ($P = 1.0000$) between the favorable outcome and unfavorable outcome groups. Among the three antifungal regimens, amphotericin B plus flucytosine had a significantly favorable outcome ($P = 0.0037$).

There were 25 HIV-negative patients and 14 (56.0%) had a favorable outcome on discharge. The mean onset age was 58 ± 14 (20–77) years and 15 (60.0%) were men. The average age of the favorable outcome group was significantly younger than that of the unfavorable outcome group ($P = 0.0416$). There were no significant differences in terms of sex ($P = 1.0000$), duration of symptoms before admission ($P = 0.9906$), symptoms include fever ($P = 1.0000$), disturbance of consciousness ($P = 0.0717$), headache ($P = 0.1833$), nausea and/or vomiting ($P = 0.0992$) and seizures ($P = 1.0000$) and underlying diseases include hypertension ($P = 1.0000$), diabetes ($P = 0.5648$), liver disease ($P = 1.0000$), renal disease ($P = 1.0000$) and autoimmune disease ($P = 1.0000$) between the favorable outcome and unfavorable outcome groups. Tuberculosis-related disease led to a significantly unfavorable outcome ($P = 0.0231$). There was no significance among the three antifungal regimens.

Laboratory findings for HIV-positive patients

Results of laboratory examinations for HIV-positive patients are shown in Table 3. For the favorable outcome group, uric acid ($P_1 = 0.0034$) and CSF chloride ($P_1 < 0.001$) were significantly increased after treatment, whereas total bilirubin ($P_1 = 0.0043$), direct bilirubin ($P_1 = 0.0323$), and CSF leukocyte count ($P_1 = 0.0164$) were significantly decreased. For the unfavorable outcome group, uric acid ($P_2 = 0.0041$), CSF LDH ($P_2 = 0.0116$, Fig. 1) and CSF chloride ($P_2 = 0.0005$) significantly increased after treatment, whereas serum albumin ($P_2 = 0.0183$) significantly decreased. For parameters before treatment, only CSF chloride ($P_3 = 0.0169$) differed significantly between the favorable outcome and unfavorable outcome groups. For parameters after treatment, there were significant differences in serum albumin ($P_4 = 0.0160$), CSF leukocyte count ($P_4 = 0.0337$) and CSF LDH ($P_4 = 0.0048$) between the favorable outcome and

unfavorable outcome groups. Increases in CD4 ($P = 0.0038$) and CD4/CD8 ratio ($P = 0.0087$) after treatment suggested favorable outcome.

3.4 Laboratory findings for HIV-negative patients

Results of laboratory examinations for HIV-negative patients are shown in Table 4. For the favorable outcome group, uric acid ($P1 = 0.0001$) and CSF chloride ($P = 0.0001$) significantly increased after treatment, whereas CSF leukocyte count ($P1 = 0.0192$) significantly decreased. For the unfavorable outcome group, only serum albumin ($P2 = 0.0008$) significantly decreased after treatment. For parameters before treatment, there were significant differences in terms of total bilirubin ($P3 = 0.0284$) and direct bilirubin ($P3 = 0.0458$) between the favorable outcome and unfavorable outcome groups. For parameters after treatment, there were significant differences in serum albumin ($P4 = 0.0199$), total bilirubin ($P4 = 0.0474$), direct bilirubin ($P4 = 0.0409$) and Qalb ($P4 = 0.0321$, Fig. 2) between the favorable outcome and unfavorable outcome groups.

Discussion

We retrospectively analyzed clinical characteristics and laboratory findings in patients with CM in a tertiary hospital in China from 2015 to 2019. Based on the prognosis on discharge, we consider that changes in Qalb value in HIV-negative patients and CSF LDH in HIV-positive patients could be potential prognostic markers.

Aging is a complex and multifaceted process that has a negative impact on the immune system and renders elderly people more susceptible to infectious diseases, including CNS infections [24, 25]. It has been reported that the clinical characteristics of elderly CM patients suggest greater vulnerability to CM [26]. In our cohort, most HIV-negative patients (13/25, 52%) were aged > 60 years (Table 1). Aging may indeed be one of the predisposing factors for CM, but a larger study is needed to confirm this. Race, living habits, and other factors should also be taken into account.

Headache, nausea and/or vomiting, and fever were the most common symptoms. However, it is difficult to distinguish bacterial, fungal and viral meningitis by such symptoms, and delay in diagnosis leads to poor prognosis [26]. Rapid diagnosis of the etiology of meningitis is needed urgently [27]. Disturbance of consciousness and seizures are considered to be poor prognostic factors for CM [28–30]. In the current study, six patients developed disturbance of consciousness before admission and all of them presented with unfavorable outcome. Similarly, 7 of 10 patients with seizures showed poor prognosis. This observation is in line with a previous study [31, 32]. Therefore, CM patients with disturbance of consciousness and/or seizures should receive more aggressive treatment and more granular monitoring.

It has been reported that reactive oxygen species play an essential role in the pathophysiology of meningitis [33]. Changes in serum antioxidant parameters such as albumin, bilirubin and uric acid may have potential as prognostic indicators [31, 32]. In our study, we found varying degrees of significance in

the comparison of the above parameters in patients before and after treatment, especially for HIV-positive patients.

HIV-positive patients are usually more likely than HIV-negative patients to have infection with opportunistic pathogens. The dominant mechanism for HIV-induced immunodeficiency is depletion and distortion of CD4⁺ T cells, and further lymphocyte defects [31, 32]. Therefore, dynamic monitoring of CD4⁺ T cell counts is critical for HIV-positive patients [34]. In our cohort, there was no significant difference in baseline CD4⁺ T cell counts at admission between favorable outcome group and unfavorable outcome group. However, the cell counts at discharge were significantly increased compared with before treatment in the favorable outcome group. Our results are consistent with previous reports [35]. Unfortunately, patients with poor prognosis often died of ineffective rescue, and the data after treatment could not be obtained.

The factors related to CSF examination for predicting unfavorable outcome of CM include high CSF opening pressure (> 250 mmH₂O), low CSF leukocyte count, high CSF CrAg titer (> 1:1024), decreased CSF glucose concentration, increased CSF protein, decreased CSF chloride and changes in CSF cytokines [28, 36–40]. LDH is ubiquitously distributed in body tissues and it contains five isoenzymes [41]. CSF LDH isoenzymes are comparable in tuberculous and pyogenic meningitis [14]. We found that an increase in CSF LDH may lead to poor outcome in HIV-positive patients (Fig. 3), but there were no similar findings in HIV-negative patients. It has been suggested that cryptococcal meningoencephalitis patients with increased Qalb tend towards a poor outcome [10]. However, that study did not distinguish between HIV-positive and HIV-negative patients. In our study, HIV-negative patients with increased Qalb had poor prognosis (Fig. 4), but the same trend was not found in HIV-positive patients.

There were several limitations to this study. First, this was a retrospective review of medical records in a single hospital. Second, the symptoms and prognosis may differ according to the different serotypes of *Cryptococcus* [42], but this was not investigated in our study. Further, large prospective multicenter studies are needed to improve the generalizability of our data on CM.

Conclusions

Due to the baseline of immune ability of HIV-infected patients differ from non-HIV-infected patients, we may need to refer to different indicators in the process of clinical treatment. Based on this study, the alternations of CSF examination items during hospitalization are of great significant to the prognosis of CM. We recommend incorporation of Qalb value analysis and pay attention to CSF LDH. Additionally, careful clinical observation is also extremely important.

Abbreviations

CM Cryptococcal meningitis

Qalb CSF/serum albumin quotient

CSF Cerebrospinal fluid

HIV Human immunodeficiency virus

LDH Lactate dehydrogenase

CNS Central nervous system

Declarations

Acknowledgments

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Ethics approval and consent to participate

The study was approved by the ethics committee of the Nanning Forth People's Hospital (no. 20210706). Informed consent was waived by the Institutional Review Board due to the retrospective nature of the study design.

Consent for publication

As this was a retrospective review that presents aggregate programme data only, consent was obtained from the local ethics review board for use of anonymized data for publication. No individual level patient data is being presented hence individual patient informed consent was deemed not necessary.

Competing interests

The authors declare no competing interests.

Availability of data materials

The data sets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HY, ZK, PW conceptualized the paper, HY drafted the manuscript, ZJ reviewed the paper, ZJ and ZK participated in the data interpretation and discussion. LH, HD and ZL participated in data analysis. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, tables 1 to 4 PDF are only available as a download in the Supplemental Files section.

Figures

Figure 1

Alternation of CSF LDH level in HIV-positive patients with unfavorable outcome. Points mark CSF LDH values of patients with unfavorable outcome before treatment, while squares indicate values of patients with unfavorable outcome after treatment. Lines present mean values and standard deviation.

Figure 2

Alternation of Qalb value in HIV-negative patients with CM after treatment. Points mark Qalb values of patients with favorable outcome, while squares indicate values of patients with unfavorable outcome after treatment. Lines present mean values and standard deviation.

Figure 3

Alternation of CSF LDH level in HIV-positive patients with CM. Red points mark values of patients with favorable outcome, while blue squares indicate values of patients with unfavorable outcome. Lines present alternations of mean values.

Figure 4

Alternation of Qalb value in HIV-negative patients with CM. Red points mark values of patients with favorable outcome, while blue squares indicate values of patients with unfavorable outcome. Lines present alternations of mean values.

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