# Cryptococcal meningitis in young adults: clinical characteristics and therapeutic outcomes

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# Abstract

Background: The clinical characteristics of cryptococcal meningitis (CM) in young adults (≤ 40 years old) have not been reported. The purpose of this study was to delineate the clinical characteristics, laboratory findings and therapeutic outcomes of young adults with CM, and compare them with older adults (> 40 years old) with CM. Methods: Ninety-nine adult patients with CM (64 men, 35 women) were enrolled from 2002-2016, of whom 26 were ≤ 40 years old (young adult group) and 73 were > 40 years old (non-young adult group). The clinical characteristics, laboratory data and therapeutic outcomes of these two groups were compared. The prognostic factors of the young adult CM patients were analyzed, and the clinical characteristics and laboratory data between the young adult CM patients with and without acquired immune-compromised syndrome (AIDS) were compared. The modified Rankin scale (mRS) was used to evaluate the outcomes of the survivors at the time of discharge and at 1 year of follow-up. Results: The young adult CM patients had a significantly higher incidence of headache as the clinical presentation. There were no significant clinical differences between the young adult CM patients with and without AIDS. There were no significant prognostic factors in the young adult CM patients, but the young adult survivors had better outcomes (mRS score 0-2) than the non-young adult group. Conclusion: The young adult CM patients had a higher incidence of headache as the clinical presentation, and the young adult CM survivors had better clinical outcomes.


# Background

Cryptococcal meningitis (CM) caused by *Cryptococcus* (*C.*) *neoformans* infection is a serious infectious disease of the central nervous system (CNS) [1, 2]. CM is associated with high rates of mortality and morbidity, and as with other CNS fungal infections, Therefore, CM has a severe economic impact on healthcare systems [2, 3]. A paediatric study of CM from China reported that the majority of patients were apparently normal, and only 23.5% had identifiable underlying conditions [4]. Paediatric cryptococcosis has been reported in both HIV-negative and -positive patients [5, 6], however other immunocompromising medical conditions are usually seen in HIV-negative patients [5]. Young adults (≤ 40 years old) are considered to be more physically healthy than very young or old individuals. Several studies have reported the clinical characteristics and therapeutic outcomes of CM [1, 2, 7-9], however the clinical characteristics and therapeutic outcomes of young adults with CM have not been examined solely in the literature. In this study, we examined the clinical and laboratory features and therapeutic outcomes of young adults with CM in order to delineate the clinical characteristics of this specific group of CM patients.

# Methods

We retrospectively reviewed the clinical manifestations, laboratory data and initial neuroimaging features of adult patients (> 18 years of age) with a new diagnosis of CM admitted to Kaohsiung Chang Gung Memorial Hospital during a 15-year study period (2002–2016). During this period, 99 adult patients with CM were identified, of whom 26 were classified into the young adult group (≤ 40 years of age) and the

other 73 were classified into the non-young adult group (> 40 years of age). The therapeutic outcomes of these patients were evaluated at discharge and at 1 year using the modified Rankin scale (mRS) [10], with the results being defined as a good outcome (mRS score = 0-2) or a poor outcome (mRS score ≥ 3). This study was approved by the Ethics Committee of Kaohsiung Chang Gung Memorial Hospital (IRB No:1608300002).

In this study, CM was defined as either (1) isolation of *C. neoformans* in one or more cerebrospinal fluid (CSF) cultures, a positive CSF cryptococcal antigen titre, or positive CSF India ink staining and clinical features of meningitis; or (2) isolation of *C. neoformans* in a blood culture with clinical presentations of meningitis and typical CSF features [1, 11]. The neuroimaging findings used for analysis were derived from initial cranial magnetic resonance imaging and/or cranial computed tomography studies as previously described [1]. During the study period, the main antifungal regimen was amphotericin B +/- flucytosine +/- fluconazole. Extra-ventricular drainage and/or ventriculo-peritoneal shunts were used to relieve hydrocephalus and/or increased intracranial pressure [1].

In this study, we performed three separate statistical analyses. First, we compared the clinical characteristics, laboratory data and neuroimaging findings between the young adult and non-young adult groups. Second, we compared the clinical characteristics and laboratory data between the young adult CM patients with and without acquired immune-compromised syndrome (AIDS). Third, we investigated the potential prognostic factors for the young adult CM patients who survived and died. Categorical variables were analyzed using the chi-square test or Fisher's exact test, and continuous variables were analyzed using the t-test or Mann-Whitney U-test. In the first analysis, variables with a $P$ value < 0.05 were further analyzed using multivariate logistic regression analysis. We also compared the mRS scores at the time of discharge and after 1 year of follow-up between the survivors in the young and non-young adult groups using the Mann-Whitney U-test.

# Results

Of the 99 included adult CM patients (64 men and 35 women), 26 were ≤ 40 years of age (young adult group) and 73 were > 40 years of age (non-young adult group). The clinical characteristics, laboratory findings and neuroimaging features of these 99 adult CM patients are listed in Table 1. The young adult group included 21 men and five women with a mean age of 30.58 years (range: 20-38 years). AIDS was the most common underlying condition in eight patients, followed by autoimmune disorders (3), hematologic disorders (2), diabetes mellitus (DM) (1), and liver cirrhosis (1). Headache was the most common clinical presentation in 23 patients, followed by fever (19), altered consciousness (8), seizure (7), visual disturbance (7), and hearing impairment (3). Table 1 also shows comparisons between the young and non-young adult groups. The result showed that gender, AIDS, DM, the presence of headache, altered consciousness, level of CSF protein, presence of Indian ink stain, and presence of cryptococcemia were all potentially different between the two groups. However, after multivariate logistic regression analysis of these potential factors, only the presence of headache was significant ($P$ = 0.047, OR = 6.228; 95% CI = 1.028-37.739).

Because eight of the 26 young adult CM patients had AIDS as the underlying condition, we compared clinical and laboratory data between the patients with and without AIDS (Table 2). The results showed that the patients with AIDS had lower CSF total protein and lactate levels, higher incidence of serum cryptococcal antigen level ≥ 1:1024, and cryptococcemia. However, none of these potential factors were significant in multivariate logistic regression analysis. Despite treatment, 10 of the 26 young adult CM patients died. Analysis of prognostic factors is shown in Table 3. The results showed that CSF/blood glucose ratio and CSF lactate level were potential factors, however none were significant in multivariate logistic regression analysis. The mRS scores of the 16 survivors in the young adult group and 50 survivors in the non-young adult group at discharge are listed in Table 4. Fifteen of the young adult CM survivors had a good outcome and one had a poor outcome at discharge and after 1 year of follow-up. With regards to the 50 non-young adult CM survivors, 29 had a good outcome and 21 had a poor outcome at discharge, compared to 28 with a good outcome and 22 with a poor outcome (including three deaths) after 1 year of follow-up. Comparisons of the median mRS scores at discharge and 1 year after discharge between the young and non-young adult CM survivors all showed significant differences (Table 4).

# Discussion

Because of the aging population worldwide, the health condition of young adults who are the cornerstone of the family and society has become more important. In this study, 80.8% (21/26) of the young adult CM patients were male, which is higher than that (58.9%, 43/73) of the non-young adult CM patients. In addition, 30.8% (8/26) of the young adult CM patients had AIDS as the underlying condition compared to only 5.5% (4/73) of the non-young adult CM patients. This is consistent with the study by Liao et al. [12] who reported that HIV seropositive CM patients in Taiwan were usually young males. In the current study, there were no significant differences in the clinical characteristics and laboratory findings between the young adult CM patients with and without AIDS (Table 2). DM is an important and rapidly growing medical disorder in Taiwan [13], and 10.9% of adults have been reported to have DM [14]. In the present study, 30.1% (22/73) of the non-young adult CM patients had DM as the underlying condition, which is higher than that (3.85%, 1/26) of the young adult CM patients. Nevertheless, there were no significant differences in the presence of AIDS or DM between the two groups of adult CM patients (Table 1). Headache was a significant factor to differentiate these two groups of adult CM patients. Headache is an important clinical manifestation of meningitis including CM [1, 15, 16] and it can be related to meningeal irritation and/or increased intracranial pressure.

The mortality rate of the young adult CM patients was 38.5% (10/26), but there were no significant prognostic factors for the survivors and non-survivors. This figure is higher than that (31.6%, 23/73) of the non-young adult group, but the difference did not reach statistical significance. Despite the higher mortality rate in the young adult CM group, unlike the non-young adult CM patients who survived, the young adult CM patients who survived at discharge had a better clinical outcome, and this better outcome was also noted 1 year after discharge from the hospital (Table 4).

## Conclusions

Compared with the non-young adult CM patients, the young adult CM patients had a significantly higher incidence of headache as the clinical presentation. Although there were differences in the underlying condition and mortality rate, these factors did not show statistical significance. However, the therapeutic and follow-up results showed that the young adult CM patient who survived had a better clinical outcome at discharge and after 1 year of follow-up compared to the non-young adult patients who survived.

## Declarations

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### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Kaohsiung Chang Gung Memorial Hospital (IRB No:1608300002). The need for informed consent was waived due to the retrospective nature of this study. The participant data was de-identified upon data collection.

### Consent for publication

Not applicable.

### Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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None

### Authors' contribution

All authors have read and approved the submitted manuscript. CWH contributed to the conception and design, data acquisition and analysis, and drafting and revision of the manuscript. CYL, JJL and WNC

contributed to the conception and design and clinical data analysis. WCT contributed to the conception and design, data analysis, and critical revision and final approval of the manuscript.

### Acknowledgements

No

## Abbreviations

CM, cryptococcal meningitis; CNS, central nervous system; CSF, cerebrospinal fluid; AIDS, acquired immune-compromised syndrome; mRS, modified Rankin scale; DM, diabetes mellitus

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# Tables

Table 1. Clinical characteristics, cerebrospinal fluid and neuroimaging data of the young adults (≤ 40 years old) with CM

| | Young adult (n=26) | Non-young adult (n=73) | p-value |
|---|---|---|---|
| Gender | | | |
| Male | 21 | 43 | |
| Female | 5 | 30 | 0.045 |
| Mortality at discharge | 10 | 23 | 0.547 |
| Underlying disease | | | |
| AIDS | 8 | 4 | 0.002 |
| Diabetes mellitus | 1 | 22 | 0.006 |
| Liver cirrhosis | 1 | 8 | 0.438 |
| Hematologic disorders | 2 | 10 | 0.727 |
| Autoimmune disorders | 3 | 7 | 0.720 |
| Malignancy | 0 | 9 | 0.107 |
| Chronic obstructive pulmonary disease | 0 | 5 | 0.322 |
| Adrenal insufficiency | 1 | 7 | 0.677 |
| Organ transplantation | 0 | 1 | 1.000 |
| Initial presentation | | | |
| Headache | 23 | 42 | 0.004 |
| Altered consciousness | 8 | 41 | 0.026 |
| Fever | 19 | 41 | 0.130 |
| Seizure | 7 | 8 | 0.063 |
| Visual disturbance | 7 | 9 | 0.119 |
| Hearing impairment | 3 | 3 | 0.184 |
| Cerebrospinal fluid (CSF) data | | | |
| White blood cell count (109/L) | 0.12 | 0.08 | 0.598 |
| CSF/ blood glucose ratio | 0.248 | 0.273 | 0.728 |
| Protein (g/L) | 0.715 | 1.208 | 0.003 |
| Lactate (mmol/L) | 4.01 | 4.52 | 0.744 |
| Indian ink | 12 | 19 | 0.018 |
| CSF Cryptococcus antigen titre (≥1024) | 14 | 24 | 0.062 |

| | | | |
|---|---|---|---|
| Positive culture result | 22 | 55 | 0.104 |
| Serum Cryptococcus antigen titre (≥1024) | 11 | 23 | 0.245 |
| Cryptococcemia | 13 | 17 | 0.011 |
| Image finding | | | |
| Basal meningeal enhancement | 10 | 24 | 0.880 |
| Pseudocyst/VRS dilatation | 5 | 27 | 0.089 |
| Hydrocephalus | 7 | 26 | 0.395 |
| Cerebral infarct | 2 | 12 | 0.505 |
| Cryptococcoma | 1 | 5 | 1.000 |

CM: cryptococcal meningitis; AIDS: acquired immunodeficiency syndrome; Ag: antigen; VRS: Virchow-Robin space

Table 2. Clinical characteristics, cerebrospinal fluid and neuroimaging data of the young adults with CM with or without AIDS

| | AIDS (n=8) | Without AIDS (n=18) | p-value |
|---|---|---|---|
| Gender | | | |
| Male | 8 | 13 | |
| Female | 0 | 5 | 0.281 |
| Mortality at discharge | 3 | 7 | 1.000 |
| Underlying disease | | | |
| Diabetes mellitus | 0 | 1 | 1.000 |
| Liver cirrhosis | 0 | 1 | 1.000 |
| Hematologic disorders | 0 | 2 | 1.000 |
| Autoimmune disorders | 0 | 3 | 0.529 |
| Adrenal insufficiency | 0 | 1 | 1.000 |
| Initial presentation | | | |
| Headache | 7 | 16 | 1.000 |
| Altered consciousness | 1 | 7 | 0.360 |
| Fever | 6 | 13 | 1.000 |
| Seizure | 1 | 6 | 0.375 |
| Visual disturbance | 2 | 5 | 1.000 |
| Hearing impairment | 0 | 3 | 0.529 |
| Cerebrospinal fluid (CSF) data | | | |
| White blood cell count (109/L) | 0.005 | 0.137 | 0.055 |
| CSF/ blood glucose ratio | 0.353 | 0.185 | 0.237 |
| Protein (g/L) | 0.51 | 0.84 | 0.024 |
| Lactate (mmol/L) | 2.90 | 5.55 | 0.011 |
| Indian ink | 5 | 7 | 0.642 |
| CSF Cryptococcus antigen titre (≥1024) | 6 | 8 | 0.388 |
| Positive culture result | 6 | 16 | 1.000 |
| Serum Cryptococcus antigen titre (≥1024) | 5 | 6 | 0.035 |
| Cryptococcemia | 7 | 6 | 0.030 |
| Image finding | | | |

| | | | |
|---|---|---|---|
| Basal meningeal enhancement | 2 | 8 | 1.000 |
| Pseudocyst/VRS dilatation | 0 | 5 | 0.281 |
| Hydrocephalus | 1 | 6 | 0.375 |
| Cerebral infarct | 1 | 1 | 1.000 |
| Cryptococcoma | 0 | 1 | 1.000 |

CM: cryptococcal meningitis; AIDS: acquired immunodeficiency syndrome; Ag: antigen; VRS: Virchow-Robin space

Table 3. Prognostic factors of the young adults (≤ 40 years old) with CM

| | Survived (n=16) | Expired (n=10) | p-value |
|---|---|---|---|
| Gender | | | |
| Male | 12 | 9 | |
| Female | 4 | 1 | 0.617 |
| Underlying disease | | | |
| AIDS | 5 | 3 | 1.000 |
| Diabetes mellitus | 0 | 1 | 0.385 |
| Liver cirrhosis | 0 | 1 | 0.385 |
| Hematologic disorders | 0 | 2 | 0.138 |
| Autoimmune disorders | 1 | 2 | 0.538 |
| Adrenal insufficiency | 1 | 0 | 1.000 |
| Initial presentation | | | |
| Headache | 14 | 9 | 1.000 |
| Altered consciousness | 3 | 5 | 0.189 |
| Fever | 11 | 8 | 0.668 |
| Seizure | 2 | 5 | 0.069 |
| Visual change | 3 | 4 | 0.369 |
| Hearing impairment | 1 | 2 | 0.538 |
| Cerebrospinal fluid (CSF) data | | | |
| White blood cell count (109/L) | 0.094 | 0.158 | 0.452 |
| CSF/ blood glucose ratio | 0.376 | 0.027 | 0.036 |
| Protein (g/L) | 0.69 | 0.76 | 0.928 |
| Lactate (mmol/L) | 3.47 | 6.45 | 0.006 |
| Indian ink | 7 | 5 | 1.000 |
| CSF Cryptococcus antigen titre (≧1024) | 8 | 6 | 0.678 |
| Positive culture result | 14 | 8 | 1.000 |
| Serum Cryptococcus antigen titre (≧1024) | 7 | 4 | 1.000 |
| Cryptococcemia | 7 | 6 | 0.420 |
| Image finding | | | |

| | | | |
|---|---|---|---|
| Basal meningeal enhancement | 8 | 2 | 0.628 |
| Pseudocyst/VRS dilatation | 1 | 4 | 0.055 |
| Hydrocephalus | 4 | 3 | 1.000 |
| Cerebral infarct | 1 | 1 | 1.000 |
| Cryptococcoma | 1 | 0 | 1.000 |

CM: cryptococcal meningitis; AIDS: acquired immunodeficiency syndrome; Ag: antigen; VRS: Virchow-Robin space

Table 4. mRS scores of the young adult and non-young adult survivors with cryptococcal meningitis

| | At discharge | | After 1 year of follow-up | |
|---|---|---|---|---|
| mRS scores | Young adult (n=16) | Non-young adult (n=50) | Young adult (n=16) | Non-young adult (n=50) |
| Good outcome | | | | |
| 0 | 12 | 18 | 11 | 17 |
| 1 | 3 | 9 | 4 | 8 |
| 2 | 0 | 2 | 0 | 3 |
| Poor outcome | | | | |
| 3 | 0 | 2 | 0 | 2 |
| 4 | 0 | 10 | 0 | 6 |
| 5 | 1 | 9 | 1 | 11 |
| 6 | 0 | 0 | 0 | 3 |
| Median mRS | 0.00 | 1.00 | 0.00 | 1.50 |
| | p=0.005 | | p=0.005 | |

mRS: modified Rankin scale