Neuro-psychological Sequelae in HIV-negative Cryptococcal Meningitis after Complete Anti-fungal Treatment

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Abstract-

Purposes: The cognitive sequelae and influence of depression in patients with cryptococcal meningitis (CM) after complete anti-fungal treatment has not been completely surveyed in literature.

Methods: Seventeen HIV-negative CM patients and 26 healthy controls were enrolled in this prospective study. Neuro-psychological evaluation was performed to assess the attention, execution, speech and language, semantic and visuo-construction function, and depression. These were correlated with longitudinal magnetic resonance imaging (MRI) through the following checklists: dilated Virchow-Robin spaces, pseudo-cysts, intra-cerebral nodule or mass, meningeal enhancement, hydrocephalus, and hyper-intensity of white matter. For cognitive outcome measurement, initial clinical and biochemical markers were collected and analyzed.

Results: The mean follow-up duration in CM patients was 69.6 months. They had impairments in attention, execution, speech and language, and visuo-construction function, while six (35%) patients fulfilled the depression criteria. Initial cryptococcal antigen titer was inversely correlated with block design score (ρ = -0.54, p< 0.05), after adjustment for depression. Patients with two or more CM-related lesions had higher CSF lactate (mean, 43.4; SD, 19.5) at baseline than those with less than two CM-related lesions (mean, 19.2; SD, 12.6) (p=0.04). CM with depression is highly associated with poor cognitive performance and higher likelihood of two or more lesions in MRI (likelihood ratio=6.012, p=0.014).

Conclusion: Cognitive deficits persist in CM patients even after complete treatment. The number of lesions plays an important role in cognitive performance and depression. Extensive involvement of the cognitive domains with wide radiographic presentations suggests a disseminated nature of cryptococcus.

Key words: HIV-negative cryptococcal meningitis, neuro-psychological sequelae

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Cryptococcal meningitis (CM), aside from tuberculosis meningitis, is a common cause of chronic meningitis[1,2]. In contrast to the Western literature, wherein CM is more commonly seen in immuno-compromised patients[3], CM patients with negative screening for human immunodeficiency virus (HIV) are repeatedly reported in Taiwan[4-6]. Anti-fungal therapy has successfully reduced the overall mortality rate but the neurologic sequelae among survivors indicates that prognosis of CM is far from being satisfactory[1,7,8].

Dementia related to CM infection is well known[9], but evidence is based on case reports[10-13] or on co-morbidity with HIV infection[14]. From these reports, the cognitive deficits ascribed to CM are mostly in the form of acute confusional psychosis, mania, or encephalopathy[10-13], aside from neurologic presentations like sensori-neural hearing loss or headache[6]. Although complete recovery of cognitive function has been reported[13], detailed neuro-psychological evaluation aimed at detecting specific cognitive deficits after complete anti-fungal treatment remains limited in current literature.

The purpose of the present study is to understand the neuro-psychological performances in CM in a steady stage and explore their relationship with initial biochemical markers and imaging findings.

METHODS

Patient enrollment

Patients with CM who were treated and discharged from the Department of Neurology, Chang Gung Memorial Hospital-Kaohsiung in the period 1997-2007, were asked to participate in this neuro-psychological follow-up examination. The diagnostic criteria of CM were according to previously published data[1]. For the 64 CM patients, 21 patients expired. Among the 43 survivors, 25 had regular follow-up at the neurology out-patient clinic. Based on the Chang Gung Memorial Hospital Ethical Committee Recommendations, all of the participants provided written informed consent.

Patients with the following conditions were excluded: 1) age <18 or >85 years; 2) evidence for alcoholism; 3) any other addictive disorders or known affective or other psychiatric diseases; 4) known neurologic disorders potentially affecting the CNS; 5) severe recent life events that might interfere with neuro-psychological testing; and 6) use of sedatives or neuroleptic medication.

For comparison, 26 subjects matched for age (54.4 year-old, SD 7.1), gender (male 19, female 7), and educational level (11.5 years, SD 2.8) were selected from the normative data as controls. None of them had a history of neurologic or neuro-psychiatric disorders, and all had normal MRI and basic blood test results (liver and renal function tests, electrolytes, and complete blood count).

Based on the inclusion and exclusion criteria, 17 patients completed the study. Demographic data were available at baseline for all patients (Table 1). Initial CSF cryptococcal antigen titer, white-cell count, CSF protein, glucose, lactate concentration, and serum sodium level were recorded as initial biochemical markers for further comparison. Moreover, creatinine level at discharge and Glasgow Coma Scale upon admission and at discharge was collected for further analysis.

Neuro-psychological testing

Neuro-psychological testing was performed in all CM patients after a mean follow-up period of 69.6± 47.5 months (range, 3-127 months). A clinical psychologist blinded to the patients' exposure status performed the tests.

The neuro-psychological battery focused on 5 cognitive functional domains: attention, execution, speech and language, memory, and visuo-construction function. Attention functions were measured by the digit span score from the Wechsler Adult Intelligence scale-III (WAIS-III)[15] and the attention and orientation score from the Cognitive Ability Screening Instrument (CASI)[16]. Executive functions were measured using the digit symbol coding, similarity, arithmetic, picture arrangement and matrix reasoning scores from WAIS-III,15 abstract thinking scores from CASI,16 and the concept, errors, and perseveration score from the Wisconsin Card Sorting Test-64 (Computer Version Scoring Program)[17].

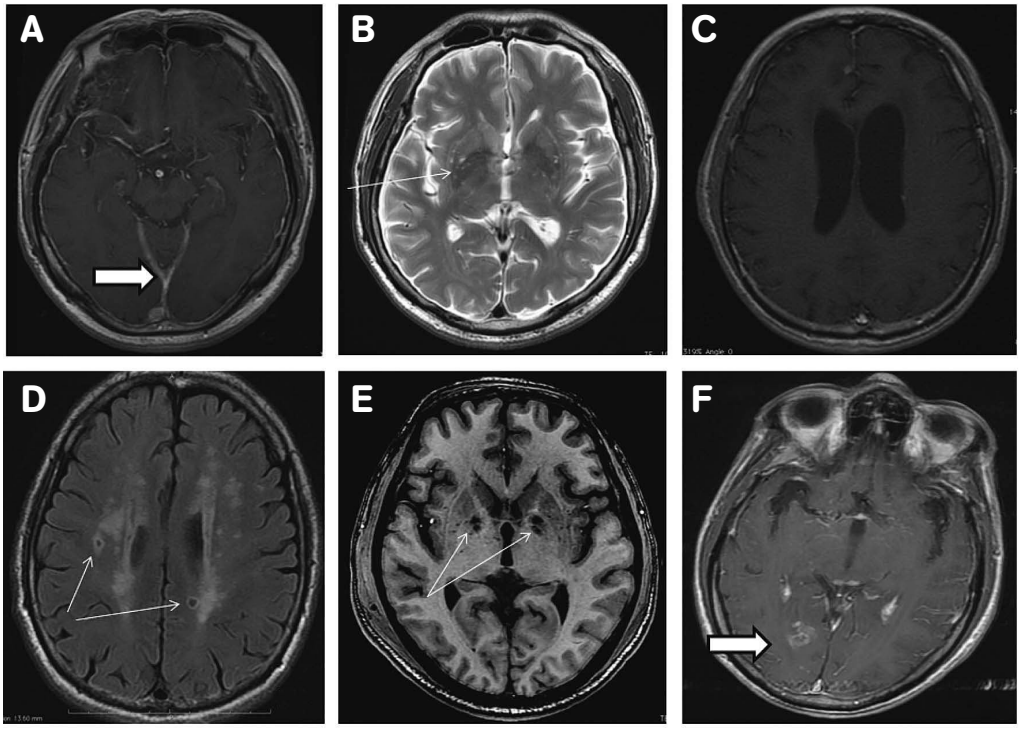

Figure 1. Magnetic resonance imaging (MRI) of Cryptococcal meningitis. (A) MRI axial T1-weighted image with Gadolinium enhancement: patchy meningeal enhancement (clear arrow). (B) MRI axial T2-weighted image: dilated Virchow-Robin spaces (arrow). (C) MRI axial T1-weighted image: hydrocephalus. (D) MRI axial FLAIR-weighted image: multiple isolated or confluent white matter changes and pseudo-cysts (arrow). (E) MRI axial T1-weighted image: Pseudo-cysts (arrow). (F) MRI axial T1-weighted image with Gadolinium enhancement: mass lesion on the right medial occipital region (clear arrow).

Memory functions were measured using the short-term and long-term memory scores from CASI 16 and the information scores from WAIS-III,15 While speech and language ability were measured using the vocabulary and comprehension scores from WAIS-III,15 and the language and semantic fluency scores from CASI[16]. Visuo-construction ability was assessed using the score of picture complete and block design from WAIS-III,15 and the drawing score from CASI[16].

The Beck Depression Inventory (BDI) Second Edition[18], a 21-item self-report instrument, was used to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition[19]. A total score of 0-13 was considered minimal range, 14-19 mild, 20-28 moderate, and 29-63 severe.

Radiologic investigations

Brain imaging studies were performed according to the clinician's decision. The last brain MRI available for each patient was less than three months of the follow-up neuro-psychological testing. All of the consecutive MRI studies were collected and analyzed by neuro-radiologists experienced in the field of central nervous system (CNS) infections but blinded to the study patients' data. Brain lesions were recorded following a pre-established check-list and CM-related lesions were defined by one of the following (Fig. 1): dilated Virchow-Robin (VR) spaces, pseudo-cyst(s), intra-cerebral nodule or mass(es), meningeal enhancement[20], hydrocephalus, and hyperintensity of the white matter[21]. Radiologic evolution was evaluated on serial brain MRI and classified as present or absent in the checklist. The intrarater reliability was examined in 20 randomly selected patients, and the kappa coefficients ranged from 0.81 to 0.88 for separate

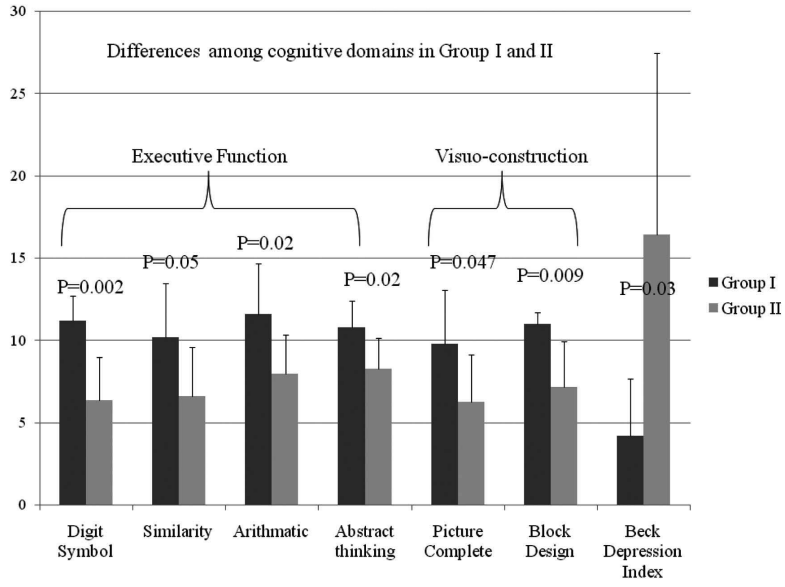

Figure 2. Differences between the Cryptococcal meningitis and control groups based on MRI findings. Bar, standard deviation; Group I, less than one cryptococcal meningitis (CM)-related lesion, Group II, two or more CM-related lesions

regions.

Statistical analyses

Data were described as mean ± standard deviation (SD). Statements on pathologic alterations in the CM group based on the neuro-psychological battery were made cautiously. They were not only based on significant group differences of the individual test results between the control and CM groups but also required significant Z-value differences in the 5 cognitive functional domains. The Mann-Whitney test was used to compare continuous variables between the control and CM groups.

To test if depression interacted with cognitive scores, the CM group was further divided into two groups using the BDI cut-off value of 13/14. A BDI score ≥14 was considered CM group with depression while a score ≥13 was considered CM group without depression. Comparisons of neuro-psychological testing between CM patients with depression and those without were analyzed by the Mann-Whitney test, and by the Kruskal-Wallis test for the two CM groups and the controls. For 2 × 2 tables, Fisher's exact test is computed with an expected frequency of less than 5. Correlation studies were calculated by the Spearman's correlation test.

Radiologic features at baseline and longitudinal follow-up were determined for all of the MR images collected. The CM-related lesions were divided into Group I with less than one CM-related lesion and Group II with two or more CM-related lesions. Comparison of biochemical markers and neuro-psychological data in these two groups were analyzed by Mann-Whitney test. All statistical data were processed by the SPSS (version 11.0 for Window; SPSS, Chicago, IL, USA). A $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and initial biochemical markers

The baseline characteristics of patients showed that none of them had HIV antibody titer above the screening threshold. Six CM patients had high initial CSF cryptococcal Ag level (≥1024) on admission, while two had elevated creatinine levels upon discharge. Using the specified BDI cut-off value, six CM patients (35.3%,

Table 1. Demographic data of cryptococcal meningitis in this study

	Depressive (n=6)	Non-depressive (n=11)	p value	Total (n=17)
Years of Education	8.5 (2.9)	11.5 (5.1)	0.1	10.4 (4.6)
Age	58.7 (8.6)	52.5 (15.2)	0.4	54.7 (13.3)
Sex (Male/Female)	6/0	10/1	1	16/1
Human Immune Virus 1 Titer (normal <1)	0.2 (0.01)	0.2 (0.02)	0.4	0.21 (0.02)
Hospitalization duration (days)	57.7 (26.9)	54.4 (36.4)	0.8	55.9 (31.1)
Glasgow Coma Scale at admission	14.7 (0.8)	13.7 (2.6)	0.4	14.1 (2.1)
Glasgow Coma Scale at discharge	14.7 (0.8)	13.7 (2.6)	0.4	14.94 (0.24)
Duration of follow-up (months)	40.7 (44.8)	85.5 (42.7)	0.06	69.6 (47.5)
CSF Cryptococcal Ag titer	450.7 (453)	1876.0 (2881.2)	0.3	16-8192
CSF White cell count (/mm^3)	72 (42.6)	217.5 (184.9)	0.1	136.7 (31.1)
CSF Protein (g/L)	3.04 (2.41)	2.15 (1.41)	0.4	2.56 (1.90)
CSF Lactate (mmol/L)	4.40 (1.62)	3.79 (2.82)	0.6	4.05 (2.30)
CSF glucose (mmol/L)	1.85 (0.55)	2.19 (1.21)	0.6	2.07 (1.01)
Serum sodium (mmol/L)	140.2 (4.0)	138.1 (4.4)	0.4	139 (4.2)
Creatinine level at discharge (μmol/L)	106.1 (35.4)	97.3 (26.5)	0.6	99.9 (26.5)
Seizure during follow up	0	0	1	0
Hydrocephalus with V-P shunting procedure	4	6	1	10
Beck Depression Index	24.8 (6.5)	4.8 (4.0)	<0.0001	11.88 (10.9)

Numbers in the parenthesis indicate standard deviation; Hospitalization duration indicates admission days related to meningitis treatment only

Abbreviations: CSF, cerebrospinal fluid; VP, ventriculo-peroneal

mild n=1; moderate n=4, severe n=1) fulfilled the depression criteria. Except for the BDI score, there were no significant differences in age, gender, education level, initial or discharge GCS score, follow-up duration, and initial biochemical markers between the depressed and non-depressed CM sub-groups (Table 1).

Neuro-psychological testing

In the 5 cognitive functional domains (Table 2), the CM group had significant differences with the control group in attention? executive function, speech and language ability, and visuo-construction function. Individual cognitive tests were also compared (Table 2).

Presence of depression affected the cognitive domains in the CM group (Table 2). The non-depressed CM patients had significantly higher score in the executive function domain and one of the visuo-construction functions. They also had significant differences with the control group in the language and speech ability (comprehension and semantic fluency) while CM patients with depression had greater impairment in the digit span, executive function (digit symbol coding, similarity, arithmetic, picture arrangement, abstract thinking, conceptual response, and non-perseveration error), short-term memory, and visuo-construction ability (picture complete and block design).

Correlation study adjusted for depression showed that initial cryptococcal antigen titer inversely correlated with block design score (ρ = -0.54, p< 0.05). There was no correlation between other biochemical markers and clinical features with neuro-psychological testing. As regards the MRI characteristics of CM patients, there were no significant differences between those with and those without depression in terms of dilated Virchow-Robin spaces, pseudo-cysts, intra-cerebral nodule or mass, meningeal enhancement, hydrocephalus, and hyper-intensity of the white matter. However, depressed CM patients had higher likelihood of having two or

Table 2. Pair-wise comparison of subsets between the cryptococcus meningitis (CM) and control groups

Cognitive function and sub-domains	CM group	Control group	p value	CM without depression (n=11)	CM with depression (n=6)	p valuea
Attention Function (Z score)	-2.14±3.4	0.12±0.6	0.002	-0.16±3.4	-2.5±3.8	0.8
Digit span	8.12±3.3**	11.73±3.6	0.002	8.91±3.2	6.67±3.4**	0.194
Attention	7.29±1.2	7.88±0.3	0.82	7.27±1.2	7.33±0.8	0.91
Orientation	15.82±3.6*	17.69±0.8	0.016	16.45±2.9	14.67±4.6	0.34
Executive Function (Z score)	-0.42±0.7	0.03±0.4	0.013	-0.07±0.6	-1.03±0.38[a]**	0.007
Digit symbol coding	8.24±3.5**	11.27±2.1	0.001	9.09±3.5	6.67±3.2**	0.2
Similarity	8.18±3.7**	11.62±1.6	<0.001	9.63±3.6	5.5±2.3[a]**	0.02
Arithmetic	9.35±3.1	10.88±2.3	0.07	10.54±3.1	7.17±1.5[a]**	0.02
Picture arrangement	7.53±3.3**	11.31±2.3	<0.001	9.82±2.1	7.67±3.0**	0.2
Matrix reasoning	9.01±2.7	9.31±2.8	0.7	10.0±2.5	7.17±2.3[a]	0.03
Abstract thinking	9.24±2.2*	10.69±1.3	0.02	9.82±2.3	8.17±1.7**	0.14
Mental Manipulation	8.59±1.6	9.35±1.1	0.7	8.64±1.7	8.50±1.5	0.9
Concept from WCST	43.02±60.0	56.19±1.79	0.4	59.03±24.4	19.01±20.5[a]**	0.006
Non-perseveration error from WCST	17.8±14.3	11.50±5.9	0.4	11.56±9.9	27.17±15.5[a]**	0.03
Perseveration error from WCST	13.1±6.8	10.62±3.4	0.4	11.89±7.1	14.83±6.6	0.4
Perseveration response from WCST	15.0±8.5	12.08±4.3	0.2	13.78±9.1	16.83±8.1	0.5
Memory Function (Z score)	-1.24±1.9	0.44±1.2	0.09	-1.25±1.86	-1.21±2.12	0.9
Short term memory	8.60±3.4	10.73±1.7	0.16	9.30±2.8	7.32±4.3*	0.9
Long term memory	9.65±0.8	9.92±0.4	0.33	9.64±0.8	9.67±0.8	0.9
Information	9.76±2.0	11.1±2.7	0.09	10.36±2.1	8.67±1.5	0.9
Speech and Language (Z score)	-0.54±1.1**	0.44±0.5	0.002	-0.51±1.13	-0.58±0.9	0.9
Vocabulary	9.06±3.6**	11.81±2.5	0.005	9.27±3.6	8.67±3.9	0.7
Comprehension	9.00±3.74**	12.54±2.7	< 0.001	9.45±3.6**	8.17±4.2	0.5
Language	9.94±0.8	9.96±0.1	0.96	9.61±0.9	9.70±0.5	0.8
Semantic fluency	6.65±2.9*	8.85±1.5	0.04	6.64±3.4*	6.67±2.3	0.9
Visuo-construction Function (Z score)	-0.65±0.8	-0.12±0.8	0.007	-0.29±00.8	-1.29±0.7[a]**	0.02
Picture Complete	7.53±3.3**	11.31±2.3	< 0.001	8.27±3.7**	6.17±1.9**	0.1
Block design	8.65±3.0**	11.73±2.4	< 0.001	10.00±2.6	6.2±2.2[a]**	0.008
Drawing	9.00±1.5	9.85±0.4	0.978	9.0±1.7	9.0±1.3	1

Data were described as mean±standard deviations; WCST: Wisconsin card sorting test

Z score, number following cognitive function; p value, between CM and control group

**p<0.01, *p<0.05 between CM and control group

ap<0.05 comparing CM group with and without depression

more MRI lesions (likelihood ratio = 6.012, p = 0.014).

Radiologic findings during the course of CM

For CM, the average imaging numbers were 4.6 times/per patient (range, 1-13, SD, 3.1). Using the MR checklist, all patients had at least one CM-related lesion in the longitudinal series, including six patients in Group I and 11 in Group II. In Group II, 10 patients received three or more MRI follow-ups. The frequencies of CM-related lesions were higher in depressed CM group than

in the non-depressed CM group (p=0.03).

The frequencies of findings were as follows (in descending order): meningeal enhancement (n=13, 76.5%, Fig. 1A), dilated VR spaces (n=10, 58.8%, Fig. 1B) and hydrocephalus (n=10, 58.8%, Fig. 1C), hyperintensity of white matter (n=8, 47%, Fig. 1D), pseudocyst(s) (n=5, 29.4%, Fig. 1E), and intra-cerebral mass(es) (n=2, 11.8%, Fig. 1F).

Relationship between cerebral images with initial biochemical markers and cognitive functions

The association of radiological features from the MRI checklist with initial biochemical markers or cognitive performance was further assessed but there was no isolated radiographic character listed in the checklist that showed group differences with the initial biochemical markers.

Group II CM patients had higher CSF lactate at baseline (mean 43.4, SD 19.5) than Group I patients (mean 19.2, SD 12.6) (p=0.04). Moreover, Group I (1 in 6) had lower frequency of VP shunt operations compared to Group II (9 in 11) (p=0.009). There are no differences between group I and group II in the initial biochemical markers, seizure, total hospitalization duration, creatinine level at discharge or GCS at admission or discharge (All P>0.05).

Comparison of neuro-psychological performances between Groups I and II showed that Group I had greater performances in executive function (digit symbol coding, similarity, arithmetic, and abstract thinking), visuo-construction (picture complete and block design) and digit span score (Fig. 2).

DISCUSSION

To date, this is the first study to explore chronic cognitive deficits in CM patients with a mean follow-up period of 69.6 months. The results show that not all patients recover to a normal state even after complete anti-fungal treatment. Furthermore, the CM group with depression has worse performance on cognitive tests, not only compared with the controls but also with the non-depressed CM group. This suggests that the presence of depression after CM is clinically important. Because of higher likelihood of MRI lesions, the presence of depression in CM patients may have a structural basis. Although complete return of cognitive function has been reported before, the present study suggests a wide spectrum and complexity of prognosis in terms of cognitive functions.

There is no published data regarding the prevalence of depression after CM although some case reports have delineated the symptoms[22,23] or considered it as a concomitant condition after HIV infection[24]. The present study shows that 35% of patients fulfilled the criteria of mild-to-severe depression. There are also no differences in demographic data and initial biomarkers between the depressed and non-depressed CM groups. Thus, it can be hypothesized from the biological basis of depression[25] in CM patients in this study that the presence of depression is associated with more CM-related MRI lesions. The biological basis of depression in CM patients is also based on poorer executive and visuo-constructive functions in the depressed CM group than in the non-depressed CM group. Correlation with dysfunctional execution may link to the frontal-sub-cortical circuits[26-28]. Structural damages, such as cerebral vasculitis[7], are common in CM patients and can occur in regions like the thalamus, basal ganglion, and cerebral cortex, which are commonly linked with depressive symptoms[29].

From the cognitive functional perspective, the CM group has impairment in attention, executive, speech and language, and visuo-construction, which are not subserved by a single network in the brain. Aside from depression, many factors may contribute to the cognitive impairments in CM patients. The current study shows that initial cryptococcal antigen titer may be the only biochemical marker predictive of cognitive performance later. High titers of cryptococcal antigen is generally considered a greater burden of yeast, poor host immune response, and greater likelihood of therapeutic failure[30].30 Another study[21] suggests a significantly positive association between the CM-related brain lesions and serum and CSF antigen titers. In contrast, the present series shows that initial CSF lactate level may be lower in patients with greater MRI lesion load. CSF lac-

tate has been associated with cerebral infarction in bacterial meningitis[31] and the level is proportional to the severity of brain injury[32,33]. Since lactate is formed during normal anaerobic glycolysis via inter-conversion of pyruvate, a rise in CSF lactate level may reflect the state of anaerobic glycolysis.

The value of longitudinal brain MRI for assessing CM-related lesions without HIV infection, along with correlation study with initial biochemical markers and cognitive performances, are analyzed in detailed here. Using MRI, all of the patients have at least one MRI finding and the positive yields of imaging abnormalities are not lower than those of CM cases with HIV infection[34,35]. From a review of longitudinal MRI in this study, lesions in CM may show worsening (enlargement or new lesions), persistence, or regression. Apparently, evolution in neuro-imaging during follow-up indicates the neurologically unstable states of CM. Thus, patients may benefit from serial radiologic evaluations from the perspective of treatment response monitoring. The present study also shows that the lesion load may greatly influence cognitive performance later. The contribution of all CM-related lesions rather than focusing on any isolated radiologic feature also point to a disseminated nature of cryptococcus.

Hydrocephalus is a common complication in CM and shunting is often considered in the clinical setting[8]. Previous study shows that early shunting in CM patients without hydrocephalus[36] may greatly improve any uncontrolled intra-cranial hypertension and outcome measures. This study is unable to definitively conclude the benefit of early shunting in cognition since none of the CM patients received VP shunting in the absence of hydrocephalus by MRI.

Several considerations may account for the higher neuro-psychological deficits in the study group despite complete treatment. First, studies by Kalita et al[37] and Lorber et al[38] demonstrate that in chronic meningitis, better cognitive performances are related to the stage of meningitis on admission. Since the study hospital is a tertiary referral center, there may be selection bias of more complicated populations in the current series, leading to the cognitive prognosis. Although early treatment is the rule of thumb[39,40], the time course of CM presentation[41] may be sub-acute or chronic, which also makes clinical judgment more difficult. Second, a more sophisticated cognitive battery, which is better suited for subtle changes in cognitive functions, is used here. Third, various pathologic changes, including white matter hyperintensities, infarction, intra-cerebral nodules, and hydrocephalus, may occur concomitantly in CM. These, in turn, influence subsequent cognitive functions. Therefore, longer follow-up periods similar to the current study may be able to present a more chronically steady state of this disorder. Lastly, treatment with anti-fungal agents may interfere with renal function and influence cognitive outcome. The present study shows that creatinine level on discharge does not correlate with cognitive performance later and suggest that the toxic effect of anti-fungal agents do not interfere with cognitive function via impaired renal function.

The present study has some limitations. First, only 17 CM patients are included. The results may not be applied to the general population for CM. Since most of the executive function tests are not different between the CM and control subjects, to conclude that the CM patients have extensive executive dysfunction still cannot be definitively stated. However, as CM patients still show significant impairment in the digit symbol coding, similarity, picture arrangement, and abstract thinking domains, it is possible that executive dysfunction may be selective, depending on the level of executive functions and complexity of the tests per se. Second, only one neuro-psychological test has been conducted during follow-up, the interpretation can only be applied on this disease stage. Lastly, because the precise duration of onset-to-treatment may be biased by the patient's drowsy consciousness on admission or the chronicity of this disease, this data cannot be obtained for further discussion. It is therefore possible that worse clinical performance in some CM patients may be due to late treatment.

In conclusion, CM patients have extensive neuro-psychological deficits even after complete anti-fungal treatment. Depression, CM-related lesions by MRI, and initial higher CSF cryptococcal antigen titer are predictive of poor cognitive performance. The extensive

involvement of cognitive domains and wide spectrum of radiographic presentations suggest a disseminated nature of cryptococcus in the brain.

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Ethics approval

The study was approved by Chang Gung Memorial Hospital's Institutional Review Committee on Human Research.

Competing interests: None

REFERENCES

1. Lu CH, Chang WN, Chang HW, Chuang YC. The prognostic factors of cryptococcal meningitis in HIV-negative patients. J Hosp Infect 1999; 42: 313-320.
2. Lu CH, Chang WN, Chang HW. The prognostic factors of adult tuberculous meningitis. Infection 2001; 29: 299-304.
3. Cunha BA. Central nervous system infections in the compromised host: a diagnostic approach. Infect Dis Clin North Am 2001; 15: 567-590.
4. Chang WN, Lu CH, Chang HW, Lui CC, Tsai NW, Huang CR, Wang HC, Chuang YC, Chen SF, Chang CC. Time course of cerebral hemodynamics in cryptococcal meningitis in HIV-negative adults. Eur J Neurol 2007; 14: 770-776.
5. Chang WN, Lu CH, Huang CR, Chuang YC, Tsai NW, Chen SF, Chang CC, Wang HC. Cerebrospinal fluid 14-3-3-gamma protein level in eight HIV-negative cryptococcal meningitis adults. Eur J Neurol 2008; 15: 428-430.
6. Wang HC, Chang WN, Lui CC, Peng JP, Huang CR, Chang HW, Liliang PC, Lu CH. The prognosis of hearing impairment complicating HIV-negative cryptococcal meningitis. Neurology 2005; 65: 320-322.
7. Lan SH, Chang WN, Lu CH, Lui CC, Chang HW. Cerebral infarction in chronic meningitis: a comparison of tuberculous meningitis and cryptococcal meningitis. QJM 2001; 94: 247-253.
8. Liliang PC, Liang CL, Chang WN, Chen HJ, Su TM, Lu K, Lu CH. Shunt surgery for hydrocephalus complicating cryptococcal meningitis in human immunodeficiency virus-negative patients. Clin Infect Dis 2003; 37: 673-678.
9. Almeida OP, Lautenschlager NT. Dementia associated with infectious diseases. Int Psychogeriatr 2005; 17: S65-S77.
10. Sa'adah MA, Araj GF, Diab SM, Nazzal M. Cryptococcal meningitis and confusional psychosis. A case report and literature review. Trop Geogr Med 1995; 47: 224-226.
11. Ala TA, Doss RC, Sullivan CJ. Reversible dementia: a case of cryptococcal meningitis masquerading as Alzheimer's disease. J Alzheimers Dis 2004; 6: 503-508.
12. Rafael H. Secondary Alzheimer started by cryptococcal meningitis. J Alzheimers Dis 2005; 7: 99-100; author reply 101.
13. Hoffmann M, Muniz J, Carroll E, De Villasante J. Cryptococcal meningitis misdiagnosed as Alzheimer's disease: complete neurological and cognitive recovery with treatment. J Alzheimers Dis 2009; 16: 517-520.
14. Gumbo T, Kadzirange G, Mielke J, Gangaidzo IT, Hakim JG. Cryptococcus neoformans meningo-encephalitis in African children with acquired immunodeficiency syndrome. Pediatr Infect Dis J 2002; 21: 54-56.
15. Wechsler D. Wechsler adult intelligence scale. Revised. 1981, New York: Psychological Cooperation.
16. Chang CC, Liu JS, Chang YY, Chang WN, Chen SS, Lee CH. (99m)Tc-ethyl cysteinate dimer brain SPECT findings in early stage of dementia with Lewy bodies and Parkinson's disease patients: a correlation with neuro-psychological tests. Eur J Neurol 2008; 15: 61-65.
17. Nyhus E, Barcelo F. The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: A critical update. Brain Cogn 2009.
18. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
19. Bourgeois M. Importance of DSM IV (APA) and ICD-10 (WHO) in diagnosis and treatment of mood disorders. Encephale 1995; 21: 47-52.
20. Lee SC, Dickson DW, Casadevall A. Pathology of cryptococcal meningo-encephalitis: analysis of 27 patients with patho-genetic implications. Hum Pathol 1996; 27: 839-847.
21. Charlier C, Dromer F, Leveque C, Chartier L, Cordoliani YS, Fontanet A, Launay O, Lortholary O. Cryptococcal neuro-radiological lesions correlate with severity during cryptococcal meningo-encephalitis in HIV-positive patients

in the HAART era. PLoS One 2008; 3: e1950.
22. Christensen A, Eikenaes E. Cryptococcal meningitis in a patient without known predisposing disease. Tidsskr Nor Laegeforen 1999; 119: 3132-3134.
23. Puccioni M, Favoreto AC, Andre C, Peixoto CA, Novis SA. Acquired immunodeficiency syndrome: analysis of neurologic complications in 44 cases. Arq Neuropsiquiatr 1989; 47: 385-391.
24. Boska MD, Mosley RL, Nawab M, Nelson JA, Zelivyanskaya M, Poluektova L, Uberti M, Dou H, Lewis TB, Gendelman HE. Advances in neuro-imaging for HIV-1 associated neurological dysfunction: clues to the diagnosis, pathogenesis and therapeutic monitoring. Curr HIV Res 2004; 2: 61-78.
25. MacQueen GM. Magnetic resonance imaging and prediction of outcome in patients with major depressive disorder. J Psychiatry Neurosci 2009; 34: 343-349.
26. Clark L, Chamberlain SR, Sahakian BJ. Neuro-cognitive mechanisms in depression: implications for treatment. Annu Rev Neurosci 2009; 32: 57-74.
27. Henry J, Crawford JR. A meta-analytic review of verbal fluency deficits in depression. J Clin Exp Neuropsychol 2005; 27: 78-101.
28. Portella MJ, Marcos T. Frontal lobe involvement in elderly major depression. Rev Neurol 2002; 35: 891-894.
29. Carlson PJ, Singh JB, Zarate CA, Jr., Drevets WC, Manji HK. Neural circuitry and neuro-plasticity in mood disorders: insights for novel therapeutic targets. Neuro Rx 2006; 3: 22-41.
30. Mitchell DH, Sorrell TC, Allworth AM, Heath CH, McGregor AR, Papanaoum K, Richards MJ, Gottlieb T. Cryptococcal disease of the CNS in immuno-competent hosts: influence of cryptococcal variety on clinical manifestations and outcome. Clin Infect Dis 1995; 20: 611-616.
31. Chang CJ, Chang WN, Huang LT, Chang YC, Huang SC, Hung PL, Ho HH, Chang CS, Wang KW, Cheng BC, Lui CC, Chang HW, Lu CH. Cerebral infarction in peri-natal and childhood bacterial meningitis. QJM 2003; 96: 755-762.
32. Inao S, Marmarou A, Clarke GD, Andersen BJ, Fatouros PP, Young HF. Production and clearance of lactate from brain tissue, cerebrospinal fluid, and serum following experimental brain injury. J Neurosurg 1988; 69: 736-744.
33. Sood SC, Gulati SC, Kumar M, Kak VK. Cerebral metabolism following brain injury. II. Lactic acid changes. Acta Neurochir (Wien) 1980; 53: 47-51.
34. Mathews VP, Alo PL, Glass JD, Kumar AJ, McArthur JC. AIDS-related CNS cryptococcosis: radiologic-pathologic correlation. AJNR Am J Neuroradiol 1992; 13: 1477-1486.
35. Miszkiel KA, Hall-Craggs MA, Miller RF, Kendall BE, Wilkinson ID, Paley MN, Harrison MJ. The spectrum of MRI findings in CNS cryptococcosis in AIDS. Clin Radiol 1996; 51: 842-850.
36. Liliang PC, Liang CL, Chang WN, Lu K, Lu CH. Use of ventriculo-peritoneal shunts to treat uncontrollable intracranial hypertension in patients who have cryptococcal meningitis without hydrocephalus. Clin Infect Dis 2002; 34: E64-E68.
37. Kalita J, Misra UK, Ranjan P. Predictors of long-term neurological sequelae of tuberculous meningitis: a multivariate analysis. Eur J Neurol 2007; 14: 33-37.
38. Lorber J. The results of treatment of 549 cases of tuberculous meningitis. Am Rev Tuberc 1954; 69: 13-25.
39. Arayawichanont A, Prayoonwiwat N, Churojana A, Sangruchi T, Poungvarin N. Successful medical treatment of multiple cryptococcomas: report of a case and literature review. J Med Assoc Thai 1999; 82: 991-999.
40. Sloan D, Dlamini S, Paul N, Dedicoat M. Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings. Cochrane Database Syst Rev 2008: CD005647.
41. Thompson HJ. Not your “typical patient”: cryptococcal meningitis in an immuno-competent patient. J Neurosci Nurs 2005; 37: 144-148.