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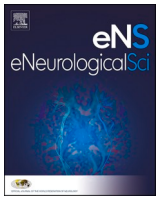

# Early diagnosis of cryptococcal meningoencephalitis in HIV-negative patients: Integration of brain MRI and clinical findings

Kosei Nakamura, Masato Kanazawa *, Yuka Koike, Takuya Konno, Osamu Onodera

*Department of Neurology, Brain Research Institute, Niigata University, Japan*

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ABSTRACT

*Purpose:* Cryptococcal meningoencephalitis (CM) in human immunodeficiency virus (HIV)-negative patients are often diagnosed later than in HIV-infected patients, which increases mortality rates concerning the former. Consequently, early diagnosis and treatment are crucial for improving clinical prognosis in HIV-negative patients. This study investigated the utility of magnetic resonance imaging (MRI) in combination with clinical and laboratory findings for early diagnosis of CM in HIV-negative patients.

*Methods:* This retrospective cohort analysis included consecutive patients diagnosed with central nervous system (CNS) infections. Demographic profiles, laboratory findings, admission symptoms, and MRI findings were assessed. A comparative analysis between CM and other CNS infections was performed.

*Results:* Twelve HIV-negative patients were diagnosed with CM, while 38 exhibited other CNS infections (two fungal, 23 bacterial, 12 viral, one parasitic). Pseudocysts on MRI ($p = 0.002$), absence of fever ($p = 0.001$), headache ($p = 0.005$), and normal C-reactive protein (CRP) levels ($p = 0.020$) were specific findings in CM. By applying a cut-off value of one point in combination of pseudocysts, absence of fever, headache, and normal CRP levels in differentiating CM from other CNS infections, the sensitivity and specificity were calculated as 76.3 % and 91.7 %, respectively.

*Conclusion:* Integrating pseudocysts, absence of fever, headache, and normal CRP levels predicts early CM diagnosis, potentially improving outcomes.

## 1. Introduction

Cryptococcus is a yeast that produces capsules. Within the genus Cryptococcus, those displaying pathogenicity in humans are primarily *C. neoformans* and C. *gattii*. However, cryptococcal infections are almost always attributed to *C. neoformans* in Japan (1). *C. neoformans* resides extensively in soil and avian excreta, particularly in pigeons. *C. neoformans* significantly predisposes individuals to meningoencephalitis owing to its neurotropic affinity. Cryptococcal meningoencephalitis (CM) is the most common cause of fungal meningoencephalitis and is commonly associated with human immunodeficiency virus (HIV) infection (2). However, in data from the French surveillance network (2005–2020), the proportion of HIV-negative patients with CM has recently surpassed that of HIV-positive patients (3). Cryptococcal meningoencephalitis can also affect immunocompromised patients, individuals with neoplastic conditions, and recipients of organ transplantation; however, it also affects those with intact immune systems (4). The diagnosis of CM is usually confirmed by cryptococcal antigen testing or cerebrospinal fluid (CSF) culture. Cryptococcal antigen testing is a specific, sensitive, and rapid test that can be performed on blood or CSF. Cryptococcal antigen testing of CSF is supported strongly by CM (5). CM, especially in HIV-negative patients, often manifests with nonspecific symptoms, including headache and impaired consciousness, sometimes leading to deferred diagnoses. The mortality rate was higher in HIV-negative cryptococcal patients than that in HIV-positive patients. Prompt identification, early diagnosis, and treatment are crucial for improving clinical prognosis in HIV-negative patients with CM.

Magnetic resonance imaging (MRI) can predict central nervous system (CNS) infectious agents. For example, fluid-fluid levels in the lateral ventricles are highly indicative of bacterial infections (6). MRI findings

*Abbreviations:* AUC, Area under the curve; CM, Cryptococcal meningoencephalitis; CNS, Central nervous system; CRP, C-reactive protein; CSF, Cerebrospinal fluid; DWI, Diffusion weighted image; FLAIR, Fluid-attenuated inversion recovery; HIV, Human immunodeficiency virus; MRI, Magnetic resonance imaging; ROC, Receiver operating characteristic.

* Corresponding author at: 1-757 Asahimachi-dohri, Niigata, Niigata 951-8585, Japan.
*E-mail address:* masa2@bri.niigata-u.ac.jp (M. Kanazawa).

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correlated with CM encompassing diverse conditions, including perivascular space (or Virchow–Robin space) dilation, meningitis, pseudocysts, granuloma, abscess, cerebral infarction, cerebral hemorrhage, hydrocephalus, and choroid plexitis (7–10). Some of these MRI findings have been postulated to mirror the distinct stages of progression of cryptococcal infection. Perivascular space dilatation, a prevailing phenomenon observed on brain MRI in CM, is hypothesized to arise from the progression of cryptococcal organisms along the perivascular spaces surrounding the penetrating arteries in deep cerebral structures, facilitated by the gelatinous mucoid material generated by these organisms. Reports on MRI of CM highlight the frequent observation of perivascular space dilation and contrast enhancement of the meninges, with pseudocysts and choroid plexitis considered relatively specific (7–9).

The diagnosis of CM may be delayed because it takes time to perform a cryptococcal antigen test. Furthermore, many patients with CNS infections present with similar symptoms, including headache, fever, and neurological symptoms. In particular, HIV-negative patients with CM develop non-specific symptoms compared with HIV-positive patients with CM. This enables a diagnosis based on physical examination alone (11). Although MRI is considered to have characteristic findings of CM, information on MRI findings in the early stages of CM in HIV-negative patients is limited. In the present study, we sought to determine whether a combination of physical examination, blood tests, and brain MRI findings at admission could identify early-stage CM before the results of antigen and culture tests.

## 2. Materials and methods

### 2.1. Patient enrollment

In this study, we conducted a retrospective analysis of the medical records of consecutive patients diagnosed with CNS infections and where the pathogen responsible for the infection was identifiable. The diagnosis of CM was established by the presence of CSF, demonstrating positivity for the cryptococcal antigen or confirmation via CSF culture, indicating the presence of cryptococci. All participants were recruited from the Niigata University Hospital between September 1997 and May 2021.

### 2.2. Clinical symptoms and laboratory studies

We investigated patient history, HIV infection, and use of immunosuppressive medications, including steroids, at the time of admission. The presence of lung lesions was evaluated in the CM group. In addition, the duration between the onset of symptoms and the start of treatment was measured. Upon admission, symptoms, including fever ($\geq$ 37.5 °C), headache, impaired consciousness, and seizures, were assessed. To evaluate patient outcomes, the Glasgow Outcome Scale was employed using a 5-point scale ranging from 1 to 5, which included the following outcomes: 1 = death, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability, and 5 = good recovery (12). We defined the poor outcome group as patients with a score of 1–3.

Blood test results upon admission included the white blood cell count ($\geq$ 10,000 /mm$^3$ defined as elevation), neutrophil, lymphocyte, blood platelet count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) (13), C-reactive protein (CRP) levels ($\geq$ 1 mg/dL defined as elevation), β-D-glucan levels ($\geq$ 11 pg/mL defined as elevation), blood cryptococcal antigen titer, and blood culture. Similarly, CSF test results upon admission included initial pressure ($\geq$ 20 cm$H_2O$ defined as elevation), cell count ($\geq$ 5 cells/mm$^3$ defined as elevation), protein count ($\geq$ 45 mg/dL defined as elevation), CSF glucose level ($\leq$ 40 mg/dL or CSF glucose/blood glucose ratio $\leq$ 0.6 defined as depressed), CSF cryptococcal antigen titer, India ink staining, and CSF culture. Items that could be evaluated quantitatively were also assessed.

### 2.3. Radiological investigations

MRI was performed using 1.5-T or 3.0-T scanners, and T1/T2-weighted images, Fluid-Attenuated Inversion Recovery (FLAIR), diffusion-weighted imaging (DWI), and contrast-enhanced T1-weighted images were evaluated. The MRI findings obtained within a few days of admission were assessed for perivascular space dilation, meningitis, pseudocysts, granuloma, abscess, cerebral infarction, cerebral hemorrhage, hydrocephalus, and choroid plexitis. Perivascular space dilation, defined as a lesion with a T2/FLAIR high signal and T1 low signal, $<$ 3 mm in size, was evaluated at the basal ganglia and centrum semiovale using a 5-grade scoring system (range 0–8) based on the number and size of lesions. A total score of 3 to 8 points was considered as having a perivascular space dilation (14–16). Meningitis was defined as leptomeningeal or dural thickening combined with focal parenchymal edema (17). Pseudocysts were defined as brain parenchymal lesions with a diameter of 3 mm or greater (15), exhibiting high signal intensity on T2-weighted images/FLAIR and low signal intensity on T1-weighted images without surrounding edema. Granulomas were defined as brain parenchymal lesions with surrounding edema. Hydrocephalus was defined as an Evans index of 0.3 or greater (18). Choroid plexitis was defined as a choroid plexus lesion with contrast enhancement. Representative MRIs are shown in Fig. 1.

### 2.4. Statistical analysis

The results were expressed as the average and standard deviation, as well as the median and quartiles. Patients were classified into two groups: the CM group and the other CNS infection group. In the comparison between the two groups, a *t*-test was used for quantitative variables with normal distribution, the Mann-Whitney *U* test for those with non-normal distribution, and the $\chi 2$ test for categorical variables. Statistical Package for the Social Sciences software (IBM SPSS version 22, IBM Inc., NY, USA) was used for these analyses. We also conducted a Receiver Operating Characteristic (ROC) analysis using GraphPad Prism version 9.5.1 (GraphPad Software, Boston, Massachusetts, USA). A $p$ value $<$0.05 was considered statistically significant.

### 2.5. Ethics compliance statement

Ethical concerns were addressed during the study. Ethics approval for this study (#2021–0183) was obtained from the Niigata University Clinical Ethics Committee.

## 3. Results

### 3.1. Patient population

Fifty patients were included in this study. Of these, 12 were diagnosed with CM, with a male to female ratio of 1:1 and an average age of 64.3 ± 18.1 years. The remaining 38 patients had other CNS infections, with a male to female ratio of 12:7 and an average age of 55.9 ± 18.3 years (Table 1). The pathogens in the other CNS infection group included two other fungi (*Candida* and *Aspergillus*), 23 bacteria, 12 viruses, and one parasite. It mentioned that specific culture tests were not performed for viruses and parasites. All patients with CM were HIV negative; 50.0 % of patients in the CM group and 15.8 % of patients in the other CNS infection groups were taking immunosuppressive drugs ($p = 0.025$). The median time from disease onset to treatment initiation was longer in the CM group at 35 days compared to 4 days in the other CNS infection group ($p = 0.007$).

### 3.2. Initial clinical symptoms and laboratory studies

Upon admission, the symptomatic manifestations suggested that the group diagnosed with CM exhibited a lower prevalence of fever (25.0 %

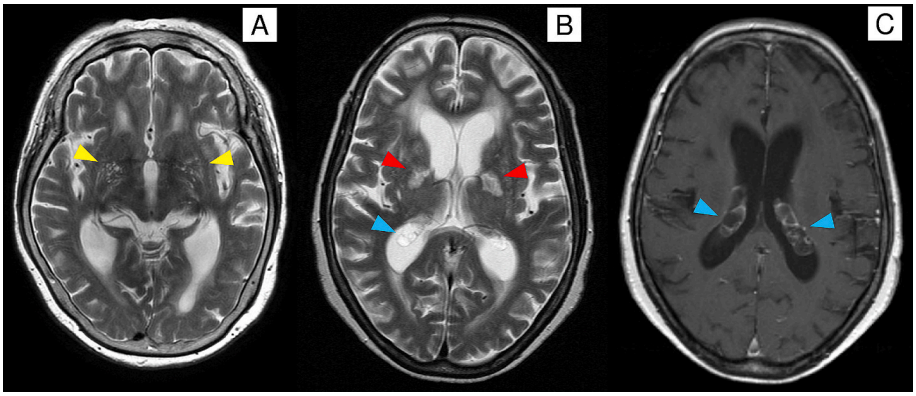


**Fig. 1.** The representative magnetic resonance images in cryptococcal meningoencephalitis.
A. Axial T2-weighted imaging, displaying bilateral perivascular space dilation (yellow arrow) in the basal ganglia. B. Axial T2-weighted imaging displaying bilateral pseudocyst (red arrow), and it showed a choroid plexus lesion (blue arrow). C. Axial T1-weighted imaging with contrast enhancement displaying choroid plexitis (blue arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 1**
General characteristics of the population.

| | CM | Other CNS infections | *p*-value |
|---|---|---|---|
| n | 12 | 38 | – |
| Age, y, mean (SD) | 64.3 (18.1) | 55.9 (18.3) | 0.180 |
| Sex, female, n (%) | 6/12 (50 %) | 14/38 (36.8 %) | 0.315 |
| HIV-positive, n (%) | 0/12 (0 %) | 1/38 (2.6 %) | – |
| Taking immunosuppressants, n (%) | 6/12 (50.0 %) | 6/38 (15.8 %) | **0.025** |
| Diabetes, n (%) | 1/12 (8.3 %) | 3/38 (7.9 %) | 0.679 |
| Pulmonary lesion, n (%) | 1/12 (8.3 %) | – | – |
| Poor outcome, n (%) | 4/12 (33.3 %) | 12/38 (31.6 %) | 0.586 |
| Time from onset of symptoms to diagnosis, days, median [IQR] | 35 [20–61.75] | 4 [2–7.5] | **0.007** |

Abbreviations: CM; cryptococcal meningoencephalitis, CNS; central nervous system, SD; standard deviation, HIV; human immunodeficiency virus, IQR; Interquartile Range.

vs. 81.6 %, $p = 0.001$) and higher prevalence of headache (75.0 % versus 26.3 %, $p = 0.005$) than the other CNS infection groups (Table 2). Qualitative evaluation revealed a difference in elevated CRP levels (25.0 % versus 65.8 %, $p = 0.020$), mononuclear cell predominance in the CSF (100 % versus. 58.8 %, $p = 0.046$), and positive rate of culture tests in the CSF (66.7 % versus 37.9 %, $p = 0.036$) between CM and other CNS infections. Quantitative tests revealed differences in median CRP value (0.42 mg/dL versus 4.61 mg/dL, $p = 0.025$).

### 3.3. Initial MRI findings

The most frequent MRI finding on admission in the CM group was perivascular space dilation (58.3 %), followed by leptomeningeal enhancement (44.4 %). Pseudocysts were more frequent in the CM group than in the other CNS infection groups (33.3 % versus 0 %, $p = 0.002$) (Table 3).

### 3.4. ROC analysis

On admission, clinical symptoms, laboratory findings, and MRI results, excluding CSF findings showed significant differences with the absence of fever, the presence of headache, normal CRP levels, and presence of pseudocysts. The patient was scored from 0 to 4 based on the following four criteria: fever, headache, CRP level, and pseudocyst on

**Table 2**
Initial symptoms and laboratory findings.

| Parameters | CM | Other CNS infections | *p*-value |
|---|---|---|---|
| Initial clinical symptoms, n (%) | | | |
| Fever | 3/12 (25.0 %) | 31/38 (81.6 %) | **0.001** |
| Headache | 9/12 (75.0 %) | 10/38 (26.3 %) | **0.005** |
| Disturbance of consciousness | 6/12(50.0 %) | 25/38 (65.8 %) | 0.496 |
| Seizure | 1/12 (8.3 %) | 6/38 (15.8 %) | 1.000 |
| Qualitative examination findings, n (%) | | | |
| Increased WBC | 3/12 (25.0 %) | 17/38 (44.7 %) | 0.317 |
| Increased CRP | 3/12 (25.0 %) | 25/38 (65.8 %) | **0.020** |
| Elevated β-D-glucan | 0/9 (0 %) | 2/13 (15.4 %) | – |
| Positive serum Cryptococcus antigen | 12/12 (100 %) | 0/13 (0 %) | – |
| Positive blood culture | 2/7 (28.6 %) | 16/29 (55.2 %) | 0.243 |
| Increased CSF pressure | 2/7 (28.6 %) | 9/24 (37.5 %) | 0.327 |
| Elevated CSF cell count | 10/12 (83.3 %) | 34/36 (94.4 %) | 0.341 |
| Mononuclear cell predominance in CSF | 10/10 (100 %) | 20/34 (58.8 %) | **0.046** |
| Elevated CSF protein | 11/12 (91.7 %) | 22/30 (73.3 %) | 0.085 |
| Decreased CSF glucose | 10/12 (83.3 %) | 26/35 (74.3 %) | 0.488 |
| Positive CSF Cryptococcus antigen | 10/10 (100 %) | 0/6 (0 %) | – |
| Positive Indian ink staining | 4/7 (57.1 %) | 0/0 (0 %) | – |
| Positive CSF culture | 8/12 (66.7 %) | 11/29 (37.9 %) | **0.036** |
| Quantitative examination findings, median [IQR] | | | |
| WBC, cells/μL | 7510.0 [4902.5–9967.5] | 8945 [6112.5–14,732.5] | 0.741 |
| Neutrophil, % | 73.6 [71.1–87.6] | 83.0 [69.5–88.9] | 0.321 |
| Lymphocyte, % | 17.4 [8.1–20.3] | 11.2 [6.2–14.8] | 0.321 |
| Platelets, *$10^4$cells/μL | 20.7 [17.7–24.6] | 19.0 [9.3–25.7] | 0.741 |
| NLR | 4.2 [3.5–11.0] | 7.3 [4.5–14.5] | 0.321 |
| PLR | 195.9 [164.3–249.1] | 182.7 [105.2–235.7] | 0.741 |
| CRP, mg/dL | 0.42 [0.11–1.09] | 4.61 [0.42–20.03] | **0.025** |
| CSF cell count, cells/μL | 104 [42.8–152.3] | 406.5 [71.8–1382.0] | 0.096 |
| CSF protein, mg/dL | 188 [133.3–309.0] | 124.5 [51.5–225.5] | 0.306 |
| CSF glucose/blood glucose | 0.33 [0.18–0.38] | 0.39 [0.21–0.48] | 0.410 |

Abbreviations: CM; cryptococcal meningoencephalitis, CNS; central nervous system, WBC; white blood cell, CRP; C-reactive protein, CSF; cerebrospinal fluid, IQR; interquartile range, NLR; neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio.

**Table 3**
Magnetic resonance imaging findings on admission.

| Parameters, n (%) | CM | other CNS infections | *p*-value |
|---|---|---|---|
| Perivascular space dilation | 7/12 (58.3 %) | 11/38 (28.9 %) | 0.089 |
| Meningitis | 4/9 (44.4 %) | 8/25 (32.0 %) | 0.716 |
| Pseudocyst | 4/12 (33.3 %) | 0/38 (0 %) | **0.002** |
| Granuloma | 1/12 (8.3 %) | 3/38 (7.9 %) | 1.000 |
| Abscess | 2/12 (16.7 %) | 18/38 (47.4 %) | 0.091 |
| Cerebral infarction | 0/12 (0 %) | 10/38 (26.3 %) | 0.092 |
| Cerebral hemorrhage | 0/12 (0 %) | 0/38 (0 %) | – |
| Hydrocephalus | 2/12 (16.7 %) | 8/38 (21.1 %) | 1.000 |
| Choroid plexitis | 3/9 (33.3 %) | 2/25 (8.0 %) | 0.102 |

Abbreviations: CM; cryptococcal meningoencephalitis, CNS; central nervous system.

**Table 4**
Diagnostic index scores for early diagnosis of cryptococcal meningoencephalitis.

| | Diagnostic index |
|---|---|
| Fever | |
| <37.5 °C | 1 |
| ≥37.5 °C | 0 |
| Headache | |
| yes | 1 |
| no | 0 |
| CRP (mg/dL) | |
| <1.0 | 1 |
| ≥1.0 | 0 |
| Pseudocyst on admission MRI | |
| yes | 1 |
| no | 0 |

Abbreviations: CRP; C-reactive protein, MRI; magnetic resonance imaging.

MRI at admission (Table 4). By applying a cut-off value of one point in the ROC analysis, the sensitivity and specificity were calculated as 76.3 % and 91.7 %, respectively, while the area under the curve was 0.91 (Fig. 2).

## 4. Discussion

We demonstrated that pseudocysts were more frequently found in the CM group than in other CNS infections. In addition to the presence of a pseudocyst on brain MRI, the absence of fever, the presence of headache, and normal CRP levels were valuable in differentiating CM from other CNS infections. The integration of these factors allows early diagnosis of CM.

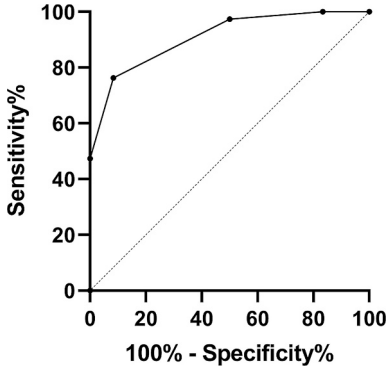


**Fig. 2.** The receiver operating characteristic curve by diagnostic index scores for early diagnosis of cryptococcal meningoencephalitis.
The receiver operating characteristic (ROC) curve by diagnostic index scores for early diagnosis of cryptococcal meningoencephalitis was shown. By applying a cut off value of one point in the ROC analysis, the sensitivity and specificity were calculated as 76.3 % and 91.7 %, respectively. Area under the ROC curve = 0.91.

The pathway through which Cryptococcus invades the brain parenchyma is postulated to involve cryptococcal entities being internalized by phagocytic cells, which then traverse the blood-brain barrier and advance into the subarachnoid space, thereby inciting meningitis (19). CM is characterized by the absence of voluminous exudates typical of purulent meningitis, and a paucity of inflammatory responses is frequently observed. Cryptococci invade the subarachnoid space and spread into the cerebral parenchyma along the perivascular space of the perforating artery. The perivascular space is enlarged by gelatinous mucus produced by the fungus, and pseudocysts may be observed in some cases. The pseudocysts sometimes appear as soap bubbles. Perivascular space dilation, which is not specific to CM, increases with age and is associated with various disorders, including cerebral small vessel disease (20), Alzheimer's disease (21), and head trauma (22). However, because the perivascular space is rarely markedly enlarged as in pseudocysts, they may be useful in diagnosing CM in HIV-negative patients.

Results from earlier physical and laboratory analyses demonstrated significant differences between CM and other CNS infections in the absence of fever, presence of headache, and normal CRP levels. The frequency of fever in CM was 72.7 % for HIV-positive ($n = 11$) patients compared to 22.2 % for HIV-negative ($n = 9$) patients (23), similar to the frequency in this study. Headache is a prevalent symptom of CM; however, it is also a common manifestation of other CNS infections. Despite the infrequent occurrence of headaches in the other CNS infection groups in the present study, it is plausible that a substantial number of patients in this group were admitted because of compromised consciousness or convulsive episodes, thereby precluding complaints of headaches. Bacterial infections result in higher CRP levels than non-bacterial infections (24), which could explain the significant difference between the CM and other CNS infection groups, including bacterial infections. Within the CM group in the present study, approximately 35 days elapsed from the commencement of symptomatic manifestations to confirmation of the diagnosis. It is plausible that the absence of pyrexia or heightened CRP levels may have influenced the time delay of diagnosis. Thus, combining this clinical information with brain MRI findings can facilitate the early diagnosis of CM.

This study had several limitations. First, we could not perform uniform MRI examinations of all patients because of the retrospective nature of the study. Second, the term "cryptococcoma" is often used in reports of CM imaging. However, this term has not been clearly defined. In this study, this term was not used. The term "pseudocyst," used in previous reports, has been included in cryptococcoma in some reports, and the lesions may not be the same as those reported here. Third, a cryptococcal antigen test or CSF culture was used to diagnose CM in this study. The cryptococcal antigen test has a high sensitivity and specificity (25), but false-positive results can occur with the fungus *Trichosporon asahii* or bacteria of the *Stomatococcus* and *Capnocytophaga* genera (26–28). However, cases diagnosed solely based on a positive cryptococcal antigen test in the CSF were not considered false positives based on the course of the cases. Additionally, we did not distinguish between C. *neoformance* and C. *gattii*. However, in Japan, C. *gattii* infection is acknowledged as an imported infectious disease and is considered extremely rare (1).

Recently, the Biofire® Film array Meningitis/Encephalitis panel has been introduced as a screening tool to search for pathogens of meningitis, and it can test for several pathogens, including Cryptococcus. However, some reports have indicated false negatives for Cryptococcus using the Biofire® Film array Meningitis/Encephalitis panel (29,30); therefore, further studies are needed.

## 5. Conclusions

Our investigation highlights the pivotal role of pseudocysts as diagnostic surrogates for discriminating between CM and alternative CNS infections in HIV-negative patients. Integration of the presence of pseudocysts in brain MRI, an absence of fever, the presence of headache, and normal CRP levels predicted early CM diagnosis. This comprehensive approach may facilitate an early diagnosis and improve patient outcomes.

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## CRediT authorship contribution statement

**Kosei Nakamura:** Writing – original draft, Investigation, Formal analysis, Conceptualization. **Masato Kanazawa:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Yuka Koike:** Writing – review & editing, Data curation. **Takuya Konno:** Writing – review & editing. **Osamu Onodera:** Writing – review & editing, Supervision, Conceptualization.

## Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Data availability

Data for this study shall be made available from the corresponding author upon reasonable request.

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