INFLAMMATORY INDEX AND TREATMENT OF BRAIN ABSCESS

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ABSTRACT

This study retrospectively analyzed 12 patients with brain abscesses. Half of the patients were diagnosed inaccurately in the initial stage, and 7.2 days were required to achieve the final diagnosis of brain abscess. The patients presented only with a moderately elevated leukocyte count, serum CRP levels, or body temperatures during the initial stage. These markers changed, first with an increase in the leukocyte count, followed by the CRP and body temperature. The degree of elevation tended to be less prominent, and the time for each inflammatory index to reach its maximum value tended to be longer in the patients without ventriculitis than in those with it.

The causative organisms of a brain abscess were detected in 10 cases. The primary causative organisms from dental caries were Streptococcus viridians or milleri, and Fusobacterium nucleatum. Nocardia sp. or farcinica were common when the abscess was found in other regions. The primary causative organisms of unrecognized sources of infection were Streptococcus milleri and Prolionibacterium sp. Nocardia is resistant to many antibiotics. However, carbapenem, tetracycline and quinolone were effective for Nocardia as well as many other kinds of bacteria.

In summary, the brain abscesses presented with only mildly elevated inflammatory markers of body temperature, leukocyte and CRP. These inflammatory markers were less obvious in the patients without ventriculitis and/or meningitis. The source of infection tended to suggest some specific primary causative organism. It was reasonable to initiate therapy with carbapenem.

Key Words: Brain abscess, Ventriculitis, Nocardia, Carbapenem, Inflammation marker

INTRODUCTION

Brain abscesses arise from a contiguous focus of infection, a direct implantation due to trauma, or a hematogenous spread from a remote site. It was reported that the direct spread from surgery, trauma, meningitis, frontal sinusitis, and dental karies was seen in 50% of patients, and that the hematogenous spread from congenital or other heart diseases, lung and abdominal abscesses was found in 32% of patients. However, 18% had abscesses of an unknown origin. Otitis media also was a direct source of infection, and septicemia or chronic bronchitis also were hematogeneous sources of infection.

The majority of cases show some evidence of a systemic infection, such as peripheral
leukocytosis, elevated C-reactive protein (CRP) values, elevated erythrocyte sedimentation rate, and elevated body temperature. However, these indicators of an infective process are not prominent in the initial stage, and a correct diagnosis is often not considered in the outpatient department or on admission. Only progressive neurological symptoms frequently prompt an urgent referral for investigation with computed tomography (CT) scanning. The difficulties in making an early diagnosis are responsible for the residual high mortality, in spite of the advent of antibiotic treatment. The best result can only be achieved if the physician remains alert to the possibility of an intracranial abscess.

The current series of 12 patients with brain abscesses retrospectively analyzed the levels and chronological changes of body temperature, leukocyte, and serum CRP for the purpose of making an early and reliable initial diagnosis. Furthermore, sources of infection and infecting organisms were also analyzed to find more information about what antibiotics should be initially selected.

CASES AND METHODS

Twelve patients with brain abscesses treated between 2006 and 2011 were retrospectively analyzed (Table 1). The patients included 10 males and 2 females whose ages ranged from 33 to 79 years old. The underlying diseases were diabetes mellitus (2 patients), chronic glomerulonephritis treated with immunosuppressant (1 patient), subarachnoid hemorrhage (1 patient), cardiac failure and pulmonary fibrosis (1 patient), and acquired immunodeficiency syndrome (AIDS, 1 patient).

The initial diagnoses in the outpatient department were brain abscess in 6 patients, cerebral infarction in 2 patients, metastatic brain tumor in 1 patient, alcohol intoxication in 1 patient, venous thrombosis in 1 patient, and simple headache in 1 patient (Table 1). The time from onset to the final diagnosis of brain abscess was 0–4 days (mean 0.8 days) in the correctly diagnosed 6 patients and 2–15 days (mean 7.2 days) in the inaccurately diagnosed 6 patients.

The frontal lobe was the most common site of the abscess (5 cases), and the other lesions were in the parietal lobe in 3 cases, basal ganglia in 2 cases, thalamus in 1 case, and cerebellum in 1 case.

A bacteriological culture was performed under an aerobic condition of 35°C for 18–24 hours with aerobic bacteria, under an anaerobic condition of 35°C for 2 days with anaerobic bacteria, and under an aerobic condition of 35°C for 3 days with . The identification of the bacterial strains was conducted using an identification kit, and the clinical isolates of were determined with a restriction fragment length polymorphism method using bacterial 16S rDNA. The microbial sensitivity test was analyzed with the microdilution method. Minimum inhibitory concentration (MIC) was measured with dry plate (Eiken Chemical Co., Ltd., Tokyo). The susceptibility was decided according to the NCCLS document.

The initial therapy was conducted with intravenous infusion of antibiotics or antimicrobials (Table 1). The secondary intravenous antibiotics or antimicrobials were administered according to the results of the microbial sensitivity test. Therapy was conducted with oral intake of antibiotics or antimicrobials in 10 cases. Excision of abscess was performed in 6 cases, and aspiration of abscess with or without decompressive craniotomy or ventricular drainage was performed in 4 cases. Ventricular drainage was performed in 1 case. One case was not treated surgically.

Ventriculitis or meningitis was diagnosed by cerebrospinal fluid analysis. Three patients developed ventriculitis and/or meningitis (ventriculitis group) and 9 cases did not (non-ventriculitis group). The inflammatory indices of body temperature, leukocyte counts, and CRP levels were analyzed and compared within each group.
### Table 1  Summary of the cases

Abbreviations: penicillin (PCG, benzylpenicillin; ABPC, ampicillin; AMPC, amoxicillin; PIPC, piperacillin), SBTPC, sultamicillin; SBT/ABPC, sulbactam/ampicillin; SBT/CPZ, sulbactam/cefoperazone), cephalosporin (CEZ, cefazolin; CTM, cefotiam; CAZ, ceftazidine; CTRX, ceftriaxone), oral cepham (CFTM, ceferam; CDTR, cefditoren; CFPM, cefcapene), oxacephem (FMOX, flomoxef), carbapenem (PAPM, panipenem; IPM, imipenem; MEPM, meropenem), aminoglycoside (TOB, tobramycin; AMK, amikacin), macrolide (EM, erythromycin; CAM, clarithromycin; CLDM, clindamycin), tetracycline (MINO, minocycline), other antibiotic (VCM, vancomycin; FOM, fosfomycin; CP, chloramphenicol; S/T, sulfamethoxazole/trimethoprim), quinolone (TFLX, tosufloxacin; LVFX, levofloxacin; PZFX, pazofoxacin).

| Case | Age | Sex | Underlying Disease | Initial Diagnosis | Time from onset to final diagnosis of brain abscess (days) | Potential entry site | Ventriculitis and/or meningitis | Primary causative organism | Antibiotics, initial oral | Operation | Outcome |
|------|-----|-----|--------------------|------------------|-------------------------------------------------------------|---------------------|---------------------------------|-----------------------------|--------------------------|-----------|---------|
| 1    | 60  | M   | Diabetes mellitus | Brain abscess    | 0                                                           | Dental caries       | Ventriculitis                   | Streptococcus viridans     | FOM, CTX                 | Ventricular drainage     | Independent gait         |
| 2    | 55  | M   | Brain metastasis | Brain abscess    | 6                                                           | Dental caries       | Ventriculitis                   | Streptococcus viridans     | MEPM                     | Resection               | Independent gait         |
| 3    | 33  | M   | Alcohol intoxication | Brain abscess | 8                                                           | Dental caries       | Ventriculitis                   | Streptococcus milleri      | SBT/ABPC, PZFX, CTRX, LVFX | Aspiration of abscess    | Independent gait, decompression craniotomy, wheelchair |
| 4    | 64  | F   | Cerebral infarction | Brain abscess | 6                                                           | Dental caries       | Ventriculitis                   | Fusobacterium nucleatum    | CLDM, SBTC/CPZ, MINO     | Resection               | Independent gait         |
| 5    | 64  | M   | Chronic glomerulonephritis intaking immunosuppressant steroid-induced diabetes mellitus | Brain abscess | 0                                                           | Lung abscess retroperitoneal abscess | Ventriculitis | Nocardia farrincina | MEPM, LVFX, MINO | Resection               | Independent gait         |
| 6    | 64  | M   | Unrecognized   | Gluteal abscess | 3                                                           | Ventriculitis       | (–)                             | Nocardia sp                  | MINO, IPM                 | Aspiration of abscess    | Independent gait         |
| 7    | 35  | M   | Subarachnoid hemorrhage hydrocephalus | Simple headache | 2                                                           | VP-shunt meningitis | Prevotella sp, Corynebacterium sp | IPM, CLDM | MINO | Resection               | Independent gait         |
| 8    | 43  | M   | Unrecognized   | Brain abscess | 1                                                           | Unrecognized       | Ventriculitis                   | Streptococcus milleri      | PAPM, ABPC, AMPC         | Aspiration of abscess    | Independent gait         |
| 9    | 53  | F   | Unrecognized   | Brain abscess | 4                                                           | Unrecognized       | Ventriculitis                   | Streptococcus milleri      | PAPM, PCG, AMPC          | Aspiration of abscess    | Independent gait         |
| 10   | 79  | M   | Cardiac failure pulmonay fibrosis | Cerebral infarction | 6                                                           | Unrecognized       | Ventriculitis                   | Propionibacterium sp       | CEZ, PIPC, EM            | Resection               | Walks with assistance    |
| 11   | 59  | M   | Unrecognized   | Brain abscess | 0                                                           | Unrecognized       | Ventriculitis                   | Propionibacterium sp       | CTX, LVFX, MINO          | No operation             | Independent gait         |
| 12   | 39  | M   | AIDS | Venous thrombosis | 15                                                          | Unrecognized       | Ventriculitis                   | Toxoplasma suspected        | CTRX, CPMP               | Resection               | Unconsciousness          |
RESULTS

Inflammation indices

The mean leukocyte count on admission was 9,694/mm\(^3\) in the non-ventriculitis group and 14,477/mm\(^3\) in the ventriculitis group (Fig. 1A). The maximum leukocyte count was 12,708/mm\(^3\) in the non-ventriculitis group and 20,747/mm\(^3\) in the ventriculitis group. The leukocyte count increased significantly after admission in the non-ventriculitis group (Wilcoxon signed-ranks test, \(p=0.028\)).

The mean serum CRP level on admission was 2.72 mg/dl in the non-ventriculitis group and 10.68 mg/dl in the ventriculitis group (Fig. 1B). The maximum CRP was 10.47 mg/dl in the non-ventriculitis group and 31.95 mg/dl in the ventriculitis group. The CRP in the non-ventriculitis group increased significantly after admission (Wilcoxon signed-ranks test, \(p=0.028\)). The maximum CRP was significantly higher in the ventriculitis group in comparison to the non-ventriculitis group (Welch's \(t\) test, \(p=0.001\)).

The mean temperature on admission was 37.3°C in the non-ventriculitis group and 37.9°C in the ventriculitis group (Fig. 1C). The maximum temperature was 38.6°C in the non-ventriculitis group and 39°C in the ventriculitis group. The temperature significantly increased after admission in the non-ventriculitis group (Wilcoxon signed-ranks test, \(p=0.011\)).

For leukocytes, the mean time for each of the indicators of infection to reach their maximum values was 10.8 days from the onset in the non-ventriculitis group and 6.7 days in the ventriculitis group. The respective values for CRP were 12.6 days in the non-ventriculitis group and 6.7 days in the ventriculitis group. In respect to body temperature, the values were 17.1 days in the non-ventriculitis group and 7 days in the ventriculitis group (no significant differences between

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![leukocyte count (\(/mm3\))](image)

**Fig. 1A** Levels of leukocyte counts at the initial stage and their maximum levels. These were analyzed separately in patients with ventriculitis and/or meningitis (ventriculitis group) and in cases without ventriculitis and meningitis (non-ventriculitis group). Black columns show mean values and bars show standard deviation. The leukocyte count increased significantly (*) after admission in the non-ventriculitis group (Wilcoxon signed-ranks test, \(p=0.028\)).
Fig. 1B  Levels of CRP at the initial stage and their maximum levels. These were analyzed separately in patients with ventriculitis and/or meningitis (ventriculitis group) and in cases without ventriculitis and meningitis (non-ventriculitis group). Black columns show mean values and bars show standard deviation. The CRP in the non-ventriculitis group increased significantly (*) after admission (Wilcoxon signed-ranks test, \( p=0.028 \)). The maximum CRP was significantly (*) higher in the ventriculitis group in comparison to the non-ventriculitis group (Welch’s \( t \) test, \( p=0.001 \)).

Fig. 1C  Levels of body temperature at the initial stage and their maximum levels. These were analyzed separately in patients with ventriculitis and/or meningitis (ventriculitis group) and in cases without ventriculitis and meningitis (non-ventriculitis group). Black columns show mean values and bars show standard deviation. The temperature significantly (*) increased after admission in the non-ventriculitis group (Wilcoxon signed-ranks test, \( p=0.011 \)).
Bacteriological findings

A hematogenous spread from a remote site was the most common cause of an abscess (11 cases). Dental caries were found in 4 cases, and the other lesions were lung and retroperitoneal abscess in 1 case and gluteal abscess in 1 case. Although the source of the infection was not recognized, hematogenous spread was suspected in another 5 cases. An abscess occurred following the infection of a ventriculoperitoneal shunt in one case of subarachnoid hemorrhage.

The causative organisms were detected in 10 cases (Table 1). The primary causative organisms were *Streptococcus viridians* (2 cases), *Streptococcus milleri* (1 case), and *Fusobacterium nucleatum* (1 case) in 4 cases of abscesses arising from dental caries. The causative organism was *Nocardia farcinica* in 1 case of retroperitoneal and lung abscess, and *Nocardia* sp. in 1 case of gluteal abscess. *Toxoplasma* infection was suggested by the MRI findings in the patient with AIDS, although no immunoserological test was performed.

Carbapenem, tetracycline, and quinolone were generally effective for many types of bacteria, including *Nocardia* (Fig. 2). Penicillin, cephalosporin, sultamicillin and macrolide were effective for many kinds of bacteria other than Nocardia. Amikacin was ineffective for *Corynebacterium* sp., *Streptococcus viridians* and *milleri*. Imipenem was ineffective for *Propionibacterium* sp., and benzylpenicillin was ineffective for *Prevotella* sp.

Outcome

Nine patients had an independent gait at discharge, but one required assistance with walking (Table 1). One patient was transferred to another hospital and required a wheelchair. The patient with AIDS was transferred to another hospital following deterioration of consciousness. That patient’s initial incorrect diagnosis resulted in a significantly poor outcome. Three of the 6 incorrectly-diagnosed patients at discharge required help with walking, needed a wheelchair,
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Streptococcus viridans

MIC (µ g/ml)

Streptococcus milleri

MIC (µ g/ml)

Corynebacterium sp.

MIC (µ g/ml)

Fusobacterium nucleatum

MIC (µ g/ml)
Fig. 2 Susceptibility test in each bacterial strain.

Abbreviations: MIC, minimum inhibitory concentration; penicillin (PCG, benzylpenicillin; ABPC, ampicillin; AMPC, amoxicillin; PIPC; piperacillin), SBTPC, sulabicillin; cephalosporin (CEZ, cefazolin; CTM, cefotiam; CTX, cefotaxime; CAZ, cefazidime; CTRX, ceftriaxone), oral cepham (CFTP, ceferam; CDTR, cefditoren; CFPM, cefcapene), oxacephem (FMOX, flomoxef), carbapenem (PAPM, panipenem; IPM, imipenem; MEMP, meropenem), aminoglycoside (TOB, tobramycin; AMK, amikacin), macrolide (EM, erythromycin; CAM, clarithromycin; CLDM, clindamycin), tetracycline (MINO, minocycline), other antibiotic (VCM, vancomycin; FOM, fosfomycin; CP, chloramphenicol), quinolone (TFLX, tosufloxacin; LVFX, levofloxacin; PZFX, pazofoxacin).
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or had consciousness disturbance (Table 2). In contrast, all 6 correctly-diagnosed patients could move about independently at discharge (\( p=0.046 \), Chi-square for independence test).

**DISCUSSION**

Headache, vomiting, drowsiness and focal symptoms, sometimes accompanied by focal or generalized seizures, are the classic symptoms of brain abscess. In addition, papilledema is commonly found in drowsy patients that appear ill.\(^1,14\) However, many individuals frequently fail to show all of these symptoms.\(^9\) In such people, the diagnosis of the brain abscess becomes very difficult. Half of the patients in the current series were diagnosed inaccurately in the initial stage, and it took 7.2 days to achieve the final diagnosis of brain abscess for the misdiagnosed patients. Bibliographically, the average time between the onset of the symptoms and confirmed diagnosis was 9.6 days.\(^{15}\)

It was reported that patients with brain abscess usually show high leukocyte counts (12,400–32,300/mm\(^3\)) at the time of admission.\(^1,8,9,16\) The CRP was elevated to a high level (2–21.6 mg/dl) in 69.2–71.4% of patients on admission.\(^7,16,17\) and 25.6–50% of abscess patients were febrile (37.8–39.8°C) at the time of admission.\(^1,8\) However, the value of these inflammatory indices were generally lower than the ones reported in the non-ventriculitis group of the current series. The mean leukocyte count, CRP level and body temperature on admission were 9,694/mm\(^3\), 2.72 mg/dl, and 37.3°C, respectively. This tendency made the initial diagnosis of brain abscess more difficult in the patients without ventriculitis. Body temperature is known to be associated with cytokine levels in serum and cerebrospinal fluid.\(^{18}\) In the current series, therefore, the inflammatory reaction was considered to be less prominent in the non-ventriculitis group than in the ventriculitis group.

Microbial infection stimulates the production of cytokines, such as interleukin-1,6,8 and TNF-alpha, in the macrophage, dendrite cells, and glial cells.\(^{16,18}\) Interleukin-6 causes a biphasic neutrophilia, wherein the first peak results from the mobilization of polymorphonuclear leukocytes into the circulating pool from the marginated pool, and the second peak results from an accelerated bone marrow release of polymorphonuclear leukocytes.\(^{19,20}\) Interleukin-1 stimulates the production of CRP in hepatocytes,\(^{16}\) and cytokines such as interleukin-1,6 and TNF-alpha act on the preoptic area of the hypothalamic thermoregulatory center and regulate body temperature.\(^{18}\) In the current series, the change of inflammatory indices began with increased leukocyte counts, followed by elevation of CRP and body temperature. The mean time for each infectious indicator to reach its maximum value in the non-ventriculitis group was 10.8 days for leukocytes, 12.6 days for CRP, and 17.1 days for body temperature. In an experiment with rabbit in which the endogeneous pyrogen was injected in to the cerebroventricular region, these inflammatory indices changed chronologically in the order of body temperature, leukocyte count, and CRP.\(^{21}\) In the current series, the pattern of chronological change of the inflammatory indices was different from

| condition at discharge | independent gait | dependent gait, wheelchair, consciousness disturbance |
|------------------------|-----------------|-----------------------------------------------------|
| correct initial diagnosis | 6               | 0                                                   |
| incorrect initial diagnosis | 3               | 3                                                   |

**Table 2** The condition at discharge in patients with correct or incorrect initial diagnosis
The initial incorrect diagnosis resulted in a significantly poor patient outcome. \(( p=0.046 \), Chi-square for independence test).
that of the rabbit experiment, but our results will help us diagnose patients correctly.

The causative organisms were reported to be eventually identified in 58–81% of cases.10,14) The majority of them were gram-positive bacteria. Anaerobes were present in 23% of patients, and meticillin-resistant *Staphylococcus aureus* or *Nocardia* were also identified in some patients.13) The source of infection tended to point toward some particular primary causative organism. It was reported that the primary causative organisms were *Streptococcus milleri*, *Staphylococcus aureus* and *Bacteroides* in dental caries, *Streptococcus milleri*, *B-haemolytic Streptococcus*, *Staphylococcus aureus* and *Bacteroides* in sinusitis, *Streptococcus* and *Proteus mirabilis* in otitis media, *Haemophilus influenza* in chronic bronchitis, and *Streptococcus milleri* and *Staphylococcus epidermidis* in infections of an unknown origin.9) In the current series, the primary causative organisms from dental caries were *Streptococcus viridians*, *Streptococcus milleri*, or *Fusobacterium nucleatum*. *Nocardia farcinica* or *Nocardia* sp. were involved when the abscess originated from other infections. The primary causative organisms were *Streptococcus milleri* and *Propionibacterium* sp. when the source of infection was unrecognized. Antibiotics must be selected during the initial stage before the bacteria are identified in a laboratory culture. These tendencies of this disease revealed in the current series will help us in the selection of appropriate antibiotics.

Optimal management of brain abscesses requires intensive antibiotic therapy,1) for which the selection of an appropriate antibiotic is crucial. The treatment has usually been performed with penicillin (benzylpenicillin) or cephalosporin (cefotaxime or ceftriaxone) in combination with vancomycin or metronidazole.22-24) Although metronidazole is stable in abscesses and a high concentration of it can be obtained from cerebrospinal fluid, its usage is not covered by Japanese national medical insurance. Furthermore, it was reported that carbapenem was more effective than the standard chemotherapy.25,26) Cure was obtained in 100% of the patients with imipenem therapy, in contrast with 86.7% of patients with the conventional chemotherapy, including penicillin and metronidazole.25) Another report also mentioned the efficacy of carbapenems (imipenem or meropenem) versus standard chemotherapy (cefotaxime and metronidazole).26) Cure was obtained in 81.8% of those on imipenem, and 96.0% of those on meropenem, in contrast with 66.7% of those cured on standard chemotherapy.26) The microbial sensitivity test in the current series also showed that carbapenem therapy is a reasonable therapeutic choice for treatment of bacterial brain abscesses, including *Nocardia* infection. Another antibiotic can be selected if there is little possibility that *Nocardia* is the cause. Penicillin, cephalosporin, sulitamicillin, and macrolide were effective for many types of bacteria other than *Nocardia* in the current series.

Nocardiosis is an opportunistic infection that has been frequently noted in patients with malignancies, systemic lupus erythematosis, long-term steroid usage, transplantation, and HIV infection.27) Our case 5 with glomerulonephritis had received corticosteroids.27) However, recent data demonstrated that central nervous system nocardiosis was common or more prevalent in patients with normal immune systems, as shown in our patient number 6.27) At any rate, nocardial brain abscesses remain a clinical challenge associated with high mortality and morbidity rates, because *Nocardia* is resistant to many antibiotics.27) The recommended treatment is usually imipenem with amikacin, ceftriaxone with amikacin, amoxicillin-clavulanate, minocycline, sulfamethoxazole/trimethoprim, sulfisoxazole, ciprofloxacin, clindamycin, linezolid, or vancomycin.23,24,28-30) In the current series, carbapenem (imipenem), tetracycline (minocycline), and quinolone (levofloxacin, pazufloxacin) proved effective for *Nocardia*.

A brain abscess has a lethal nature despite recent advances in its diagnosis and treatment.2) The total mortality rate was reported to be 18–44.7%,2,3,5) Poor prognostic factors were prominent consciousness disturbance at admission, an age below 2 years, and multiple abscesses.2,5) The causative organisms also affect the results. Fungus and aerobic bacteria were related to poor outcomes.3,15) In the current series, initial incorrect diagnoses resulted in significantly poor
outcomes. The delay in making a diagnosis allows time for the rapid enlargement of the brain abscess and causes consciousness disturbance. Therefore, the early diagnosis of brain abscess, proper estimation of causative organisms from the source of infection, and appropriate usage of antibiotics are mandatory.

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