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Original Article

Clinical Characteristics of Fusobacterial Brain Abscess

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SUMMARY: We retrospectively reviewed 122 patients with culture-proven bacterial brain abscesses (BBA) at our hospital over a period of 20 years and identified seven fusobacterial brain abscess patients. Here we describe the therapeutic experience in fusobacterial BBA cases and compare the clinical features of patients with single pathogen infection between fusobacterial and non-fusobacterial brain abscesses. *Fusobacterium* spp. accounted for 6% of the implicated pathogens of monomicrobial BBA. All seven fusobacterial brain abscess patients contracted the infection spontaneously, and two cases had important preceding events. *F. nucleatum* was the commonest one of the species described. Clinical presentations and laboratory data of these seven patients were similar to those of non-fusobacterial BBA, and in these patients the diagnosis was only confirmed by positive culture results. All seven patients were successfully treated with combined surgical and antimicrobial therapy. Although the average age tends to be older and there is a higher prevalence of multiloculated brain abscesses in patients with this type of BBA, the therapeutic outcome can be favorable with early diagnosis and prompt treatment.

INTRODUCTION

A brain abscess is a focal brain parenchymal infection caused by microorganisms. Despite the advent of new antimicrobial agents, new neuroimaging studies, and modern neurosurgical techniques, a brain abscess remains a potentially fatal infectious disease. *Fusobacterium* spp. are an anaerobic Gram-negative bacilli with fusiform morphology. Of the *Fusobacterium* spp., *F. nucleatum*, *F. necrophorum*, *F. mortiferum* and *F. varium* are the main subtypes involved in clinical infections (1), and *F. nucleatum* is the one mainly associated with infections of the mouth, lungs, and brain (2). *Fusobacterium* spp. are frequently isolated from abscesses, obstetric and gynecologic infections, blood and wounds, and as a causative pathogen of brain abscesses (3-8).

To our knowledge, only a few case report studies (9-11) have focused specifically on bacterial brain abscesses (BBA) caused by *Fusobacterium* spp. In this study, we aimed to analyze the clinical characteristics, laboratory data, and therapeutic outcomes in seven patients with monomicrobial BBA caused by *Fusobacterium* spp. as well as the causative agents of monomicrobial BBA and mortality case numbers in each species. We also compared patients with single pathogen infection between fusobacterial and non-fusobacterial brain abscesses.

PATIENTS AND METHODS

Over a period of 20 years (1986-2005), 122 patients (92 males and 30 females; age range, 10 days-84 years) with culture-proven BBA were identified at the Chang Gung Memorial Hospital (CGMH)-Kaohsiung, Taiwan. CGMH-Kaohsiung, the largest medical center in southern Taiwan, is a 2,482-bed teaching hospital that serves as a primary and tertiary referral care teaching hospital. Among the 122 cases, 98 had a single pathogen infection and 24 had polymicrobial infection. Of the 98 cases with single pathogen infection, seven had *Fusobacterium* spp. infection, and all of these patients were enrolled in this study. *Fusobacterium* spp. infection was involved in four of the 24 cases with polymicrobial infection.

In this study, a diagnosis of culture-proven BBA was made if a patient had: (i) classic neurologic manifestations of BBA including headache, fever, focal signs, and consciousness disturbance; (ii) characteristic neuroimaging (computerized tomography [CT] and/or magnetic resonance imaging [MRI]) findings of BBA; and (iii) positive pathogen(s) isolation from blood, pus, and/or cerebrospinal fluid (CSF) (12). We analyzed the clinical features, laboratory data, and therapeutic outcomes of the seven monomicrobial *Fusobacterium* spp. cases.

In our hospital, anaerobic cultures were processed in Brucella agar plates, Bacteroides bile esculin agar/phenylethyl alcohol blood agar media, and thioglycolate broths. *Fusobacterium* spp. were identified initially by their colonial and microscopic morphology. Further subtyping was conducted using the RapID-ANA II System (Remel, Inc., Lenexa, Kans., USA). Antibiotic susceptibility of the isolated *Fusobacterium* spp. was tested by two endpoint-determining susceptibility testing methods (supplemented Brucella agar).

To compare changes over time, we divided the appearance of disease among our patients into two time periods in which each encompassed 50% of the observation period. The first time period of 10 years was from January 1986 to December 1995, and the second time period, also covering 10 years, was from January 1996 to December 2005. A combination of surgical intervention and antibiotic therapy were the mainstay of treatment for BBA. The final choice of antibiotics was guided by the final culture results, while surgical procedures used in the treatment included aspiration and/or evacuation that was determined by the location, number, and configura-

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Table 1. Basic clinical data of patients

Pts	Age/ Sex	Underlying condition	Isolated pathogen (culture origin)	Clinical manifestation	GCS on admission	Leuko-cytosis	Location and features of neuroimage findings	Surgical treatment	Antibiotic treatment intravenously (days)	Therapeutic outcome
1	71/F	Diabetes mellitus	*F. nucleatum* (pus)	Headache, fever, seizure, visual disturbance, hemiparesis	15	N	Right parietal lobe, multiloculated	Aspiration	P 18×10^6 u/day + C 4 g/day (35)	Survived, hemiparesis
2	40/M	COM	*F. necrophorum* (pus)	Headache, fever, vomiting, consciousness disturbance, hemiparesis, stiff neck	9	Y	Right temporal lobe, uniloculated	Evacuation	P 18×10^6 u/day + MET 3 g/day (35)	Survived, total recovery
3	58/M	Unknown	*F. nucleatum* (pus)	Headache, fever, visual disturbance, stiff neck	15	Y	Left occipital lobe, uniloculated	Evacuation	P 18×10^6 u/day + C 4 g/day (28)	Survived, hemiparesis and homonymous hemianopia
4	64/M	Chronic hepatitis	*F. nucleatum* (pus)	Fever, seizure	15	N	Left frontal lobe, uniloculated	Evacuation	P 18×10^6 u/day + C 4 g/day (28)	Survived, total recovery
5	34/M	Unknown	*F. nucleatum* (pus; CSF)	Headache, fever, vomiting, stiff neck	15	Y	Right frontal lobe, multiloculated,	Aspiration and EVD[1)]	CRO 4 g/day+ MET 1.5 g/day (48)	Survived, total recovery
6	52/M	Unknown	*F. nucleatum* (pus)	Hemiparesis	15	Y	Left parietal lobe, uniloculated	Aspiration, then evacuation	MET 2 g/day + CRO 4 g/day (60)	Survived, wheelchair-bound
7	51/M	Sinusitis and mastoiditis, NPC s/p R/T	*F. nucleatum* (blood)	Fever, consciousness disturbance	11	Y	Left temporal lobe, multiple and multiloculated	Evacuation	MET 1.5 g/day+ CRO 4 g/day + Va 2 g/day (28)	Survived, total recovery

[1)]: Concomitant meningitis and hydrocephalus.

Pts, patient number; GCS, Glasgow coma scale; M, male; F, female; COM, chronic otitis media; NPC, nasopharyngeal carcinoma; s/p, status post; R/T, radiotherapy; CSF, cerebrospinal fluid; Y, yes; N, no; EVD, extraventricular drainage; C, chloramphenicol; CRO, ceftriaxone; MET, metronidazole; P, penicillin G; Va, vancomycin.

tion of the abscess(es), as well as the general medical condition of the patient. In this study, the therapeutic outcome of each patient was evaluated on the third month after discharge.

RESULTS

The clinical features, laboratory data, and therapeutic outcomes of the seven monomicrobial fusobacterial brain abscess cases are listed in Table 1. The seven cases consisted of six males and a female, with an age range of 34 to 71 years (mean, 52.9 years). Of the seven cases, underlying medical conditions were found in four cases, including chronic otitis media (1), hepatitis C (1), nasopharyngeal carcinoma associated with sinusitis and mastoiditis (1), and diabetes mellitus (1). None of the patients received dental manipulation or any surgical procedure in the preceding 3 months before the development of BBA.

Of the clinical manifestations, fever (6) was the most common, followed by headache (4), motor weakness (3), neck stiffness (3), vomiting (2), visual disturbance (2), seizures (2), and consciousness disturbance (2). The time intervals between the onset of symptoms and the diagnosis of brain abscess and between the onset of symptoms and surgical intervention were ranged from 3 to 24 days (10.3 ± 7.7 days) and from 7 to 28 days (13.3 ± 7.7 days), respectively. On admission, leukocytosis was found in five patients, while neuroimaging findings of all seven enrolled patients showed supratentorially located abscesses, with diameters ranging from 2.5 to 4.8 cm. Only one, Patient 7, had multiple abscesses. Multiloculated abscesses were found in Patients 1, 5, and 7 (Fig. 1A and B).

The implicated *Fusobacterium* spp. of these seven cases were cultured from brain abscesses in six cases (Patients 1 - 6) and from blood samples in Patient 7. Of these, six were *F. nucleatum* and one was *F. necrophorum*. Two cases received antibiotic therapy before the abscess cultures were made available, one for 24 h (Patient 1, penicillin G + chloramphenicol) and the other for 72 h (Patient 7, ceftriaxone + vancomycin + metronidazole). However, both had the blood cultures performed prior to antibiotic therapy. The antibiogram of the seven cultured fusobacterial strains are listed in Table 2, and all showed susceptibility to both penicillin G and chloramphenicol.

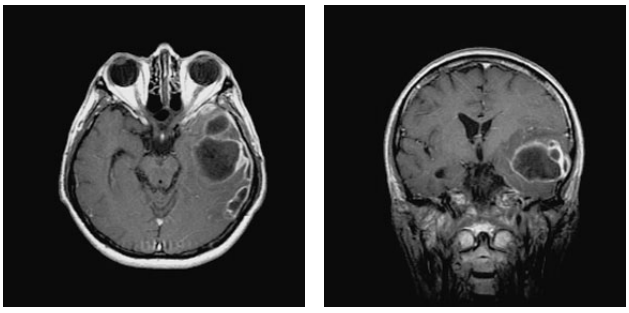

Fig. 1. Brain magnetic resonance imaging scan T1-weighted MRI axial view (A) and coronal view (B) post-Gadolinium-DTPA administration shows multiple and multiloculated abscesses at the left temporal lobe.

All seven cases received both neurosurgical and antimicrobial therapy. The antimicrobial regimens used in the treatment of these seven cases are listed in Table 1, and the duration of treatment ranged from 28 to 60 days. Of the neurosurgical procedures, Patients 1 and 5 underwent aspiration therapy, while Patients 2 - 4 and 7 underwent evacuation therapy. Patient 6 received aspiration therapy initially, but evacuation therapy was performed 47 days later due to persistent fever and poor recovery of neurologic condition. Patient 5 also underwent extraventricular drainage because of concomitant meningitis and hydrocephalus. The duration of hospitalization ranged from 14 to 71 days, and all seven patients survived. Four cases (Patients 2, 4, 5, and 7) had full recovery, while two (Patients 1 and 3) had hemiparesis. Patient 6 was discharged in a wheelchair-bound status.

The transition of prevalence of bacterial species during the study period is listed in Table 3. In the first study period, 84% (47/56) of cases were infected by a single pathogen, with Gram-negative bacilli being the most prevalent (36%,

Table 2. Antibiotic susceptibility patterns of *Fusobacterium* spp. isolates

Patient No.	Pathogen	Antibiogram											
		TIC	E	LOX	TE	CF	P	PIP	C	CC	AmC	MET	FLO
1	*F. nucleatum* (pus)	S	R	S	S	S	S	S	S	R	–	–	–
2	*F. necrophorum* (pus)	S	S	S	S	S	S	S	S	S	–	–	–
3	*F. nucleatum* (pus)	–	–	–	–	–	S	S	S	S	S	S	S
4	*F. nucleatum* (pus)	–	–	–	–	–	S	S	S	S	S	S	S
5	*F. nucleatum* (pus, CSF)	–	–	–	–	–	S	S	S	S	S	S	S
6	*F. nucleatum* (pus)	–	–	–	–	–	S	S	S	S	S	S	S
7	*F. nucleatum* (blood)	–	–	–	–	–	S	S	S	S	S	S	S

S, sensitive; R, resistant; TIC, ticacillin; E, erythromycin; LOX, moxalactam; TE, tetracycline; CF, cephalothin; P, penicillin G; PIP, piperacillin; C, chloramphenicol; CC, clindamycin; AmC, amoxicillin/clavulanic acid, MET, metronidazole; FLO, flumarin; CSF, cerebrospinal fluid; –, not done.

Table 3. Causative pathogens of bacterial brain abscesses (January 1986 - December 2005)

Organism	1986 - 1995	1996 - 2005
	n = 56 (21)	*n* = 66 (17)
Gram-negative bacilli (*n* = 37)		
Klebsiella pneumonia	7 (5)	10 (4)
Pseudomonas aeruginosa	2 (0)	2 (1)
Salmonella spp.	2 (0)	0
Proteus mirabilis	2 (0)	0
Enterobacter cloacae	1 (0)	2 (1)
Escherichia coli	1 (1)	1 (0)
Vibrio cholerae non-O1	1 (1)	0
Klebsiella oxytoca	1 (0)	0
Acinetobacter baumannii	0	3 (0)
Serratia marcescens	0	2 (0)
Streptococcus spp. (*n* = 28)		
Viridans streptococci	10 (3)	16 (3)
Group B *Streptococcus*	0	1 (0)
Non-A, non-B, and non-D *streptococci*	0	1 (0)
Staphylococcus spp. (*n* = 9)		
Staphylococcus aureus	3 (1)	3 (0)
Coagulase-negative *Staphylococcus*	3 (2)	0
Anaerobes (*n* = 24)		
Bacteroides spp.	6 (1)	0
Corynebacterium spp.	3 (1)	0
Peptococcus spp.	3 (2)	0
Fusobacterium spp.	2 (0)	5 (0)
Peptostreptococcus spp.	0	3 (0)
Pasteurella spp.	0	1 (1)
Propriobacterium acne	0	1 (0)
Mixed infection (*n* = 24)	9 (4)	15[1)](7[2)])

[1)]: Four patients had mixed infection including *Fusobacterium* spp.
[2)]: One patient had mixed infection including *Fusobacterium* spp.
( ), number of death.

17/47), followed by anaerobes (30%, 14/47), *Streptococcus* spp. (21%, 10/47), and *Staphylococcus* spp. (13%, 6/47). In the second study period, 77% (51/66) of cases were infected by a single pathogen, with Gram-negative bacilli again being the most prevalent (39%, 20/51), followed by *Streptococcus* spp. (35%, 18/51), anaerobes (20%, 10/51), and *Staphylococcus* spp. (6%, 3/51). Among the anaerobic pathogens, *Bacteroides* spp. (42.9%, 6/14) was the most common during the first study period and *Fusobacterium* spp. (50%, 5/10) in the second study period.

The mortality rate of the fusobacterial and non-fusobacterial BBA group was 0 and 26.4% (24/91), respectively. The mortality rates of patients classified by different groups of causative organisms were as follows: Gram-negative bacilli, 35% (13/37); *Streptococcus* spp., 21% (6/28); *Staphylococcus* spp., 33% (3/9); anaerobic pathogens, 29% (5/17); and mixed bacterial infections, 46% (11/24).

Table 4. Comparisons of clinical features and neuroimaging findings in single pathogen infection between fusobacterial and non-fusobacterial brain abscesses

	Fusobacterial brain abscess *n* = 7 (%)	Non-fusobacterial brain abscess *n* = 91 (%)
Sex (M/F)	6/1	65/26
Mean age (mean ± SD)	52.9 ± 12.9	44.6 ± 18.4
Mental state at the time of admission		
Clear consciousness (GCS=15)	5 (71.4)	44 (48.4)
Disturbed consciousness (GCS<15)	2 (28.6)	47 (51.6)
Interval between onset of symptoms and diagnosis of abscess	10.3 ± 7.7	15.4 ± 18.8
Underlying diseases		
Congenital heart diseases	0 (0)	10 (11.0)
Diabetes mellitus	1 (14.3)	21 (23.1)
Alcoholism/liver cirrhosis	0 (0)	12 (13.2)
Chronic otitis media	1 (14.3)	11 (12.1)
Clinical features		
Fever	6 (85.7)	54 (59.3)
Headache	4 (57.1)	47 (51.6)
Hemiparesis	3 (42.9)	44 (48.4)
Nausea/vomiting	2 (28.6)	21 (23.1)
Neck stiffness	3 (42.9)	28 (30.8)
Seizure	2 (28.6)	13 (14.3)
Hydrocephalus	1 (14.3)	16 (17.6)
Septic shock	0 (0)	16 (17.6)
Visual disturbance	2 (28.6)	13 (14.3)
Papilloedema	0 (0)	5 (5.5)
Hemiparesthesia	0 (0)	14 (15.4)
Associated with meningitis	1 (14.3)	14 (15.4)
Portal of entry		
Hematogenous spread	1 (14.3)	27 (29.7)
Non-hematogenous spread	6 (85.7)	64 (70.3)
Acquisition of infection		
Nosocomially acquired	0 (0)	24 (26.4)
Community acquired	7 (100)	67 (73.6)
Neuroimaging findings		
Nearest distance between the ventricular wall and margin of brain abscess	15.4 ± 9.1	12.1 ± 12.0
Size of the nearest brain abscess	33.0 ± 8.3	39.0 ± 19.3
Multiloculation	3 (42.8)	21 (23.1)
Mortality	0 (0)	24 (26.4)

The comparisons of clinical features and neuroimaging findings of patients with single pathogen infection between

fusobacterial and non-fusobacterial brain abscesses are listed in Table 4. From the data there, one can conclude that the patient with a fusobacterial brain abscess has an older age of onset, higher percentage likelihood of clear consciousness on admission, shorter interval between onset of symptoms and diagnosis of abscesses, higher incidence of fever as the presenting symptom, and higher incidence of multiloculation.

DISCUSSION

Many factors influence the contributive frequency of anaerobic pathogens in BBA (3,5,13-16), and anaerobic pathogens have been implicated in 21.4 to 67% of cases (4-6,10,14). In this study, *Fusobacterium* spp. accounted for 6% (7/98) of the implicated pathogens in monomicrobial BBA and in 17% (4/24) of polymicrobial BBA. Among the implicated *Fusobacterium* spp., *F. nucleatum* was the most common, accounting for 86% (6/7) of cases. The other species was *F. necrophorum* (1/7, 14%). These incidence rates are similar to those noted in other reports (6,9,18,19) and reflect the finding that *F. nucleatum* is the predominant *Fusobacterium* spp. from clinical specimens (1).

In Han's study, monomicrobial infection was seen in one of five (20%) cases of fusobacterial BBA (9). However, in this study, 64% (7/11) of fusobacterial infections were monomicrobial. We cannot conclude that this difference in incidence of *Fusobacterium* spp. in monomicrobial and polymicrobial BBA is due to a small case number in both studies.

Possible predisposing factors were present in two patients: one with chronic otitis media (Patient 1) and the other with sinusitis and mastoiditis (Patient 7), which are recognized as predisposing factors for brain abscess. Patient 7, with a "sterile" brain abscess, had fusobacterial bacteremia. This may be due to the fact that blood cultures and abscess cultures were done at different time points. In this case, the blood culture was performed before antibiotic therapy, while the abscess culture was performed 72 h after preoperation antibiotic therapy.

Pre-culture antibiotic therapy can reduce the positive culture rate (17). Although *Fusobacterium* spp. is a well-known cause of periodontal disease (2), no one was recorded with dental diseases in our study. Because dental examinations are routine examinations in BBA patients with asymptomatic dental disease and most patients with periodontitis are asymptomatic (18), whether asymptomatic periodontitis can cause brain abscess or not needs further investigation. While post-neurosurgical conditions play an increasing role in central nervous system infection (8), this was not the case in fusobacterial brain abscesses in our study patients.

As to clinical manifestations, fever was the most common (86%, 6/7), followed by headache (57%, 4/7), and hemiparesis (43%, 3/7). Fever was more common in fusobacterial brain abscesses than in other monomicrobial brain abscesses in the present study. However, these manifestations are not unique and can be found in BBA, which can be due to other pathogens. Therefore, the diagnosis of fusobacterial brain abscess can only be confirmed by a positive culture result.

As this study has shown, 42.8% (3/7) of the abscesses were multiloculated, the incidence of which was higher than the incidence among the overall BBA (10 - 20%) (19-22) or monomicrobial (23% in present study, Table 4) BBA. Many factors influence abscess encapsulation, including the offending organism, origin of infection (direct extension versus metastatic), host immune status, corticosteroid use, and antibiotic therapy (23). A variety of enzymatic tissue-active toxins that are produced by microorganisms (e.g., *B. fragilis*) also play important roles in lyses of the capsule (e.g., collagenase) and abscess expansion (e.g., hyaluronidase) (24). *F. nucleatum* and *F. necrophorum* have been reported to have the ability to induce epithelial cells to produce collagenase 3. Whether they can induce the fibroblast, neurons, glial cells, or inflammatory cells to produce collagenase 3 needs further study, although there seems to be a potential role in multiloculation (25).

As shown in this study, the clinical manifestations and therapeutic outcome of the three cases with multiloculated fusobacterial brain abscess are similar to those of the other four cases with uniloculated fusobacterial brain abscesses. We noted a similar mortality rate between multi- and uniloculated BBA in our previous report (22). Because of the limitation of the small case number, the clinical characteristics of fusobacterial brain abscesses require further large-scale investigation.

Because of complex situations, like different therapeutic regimens and co-morbidities, it is difficult to conduct any real statistical analysis of prognostic factors of BBA patients. However, with both antimicrobial and neurosurgical interventions, all seven fusobacterial BBA cases in the present study survived. Three cases from the literature concerning isolated, single fusobacterial brain abscess also survived (9-11). These patients' other clinical features are listed in Table 5. The high survival rate (100%) of fusobacterial BBA in our study may be due to the early diagnosis, relatively better

Table 5. Clinical data of bacterial brain abscess caused by single *Fusobacterium* spp. in English medical literature

Pt	Age/ Sex	Underlyng condition	Isolated pathogen (culture origin)	Clinical manifestations	Leuko-cytosis	Location and features of neuroimage findings	Surgical treatment	Antibiotic treatment (days)	Interval between sympotom and onset of Abx/to surgery (days)	Reference
1	45/M	?	*F. necrophorum* (pus)	Headache, short term memory loss, slurred speech, fever, meningism	?	One uniloculated abscess, left parietal	Evacuation followed by aspiration	P + MET + CRO (?)	65 (post-op)/65	Han et al. (9)
2	59/F	Moderate alcohol consumption	*F. nucleatum* (CSF by PCR)	Fever, consciousness disturbance, stiff neck	?	Nine abscesses, meningitis	Nil	CRO + fosfomycin + MET (28)	?/?	Heckmann et al. (10)
3	28/M	COM, sinusitis	*F. nucleatum* (pus)	Headache, seizure, hemi-hypoesthesia, hemiparesis, consciousness disturbance, bilateral auditory impairment	N	One multiloculated, left parietal, gas-fluid level with RIV	Aspiration, penicillin irrigation, closed drainage	P + C (?)	18 (post-op)/21	Taguchi et al. (11)

Pt, patient; M, male; F, female; COM, chronic otitis media; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; ?, not clear from the literature; N, no; RIV, rupture into ventricle; C, chloramphenicol; CRO, ceftriaxone; P, penicillin G; MET, metronidazole; Abx, antibiotic treatment.

mental and neurologic status on admission (12), choice of neurosurgical procedures, and use of suitable antimicrobial therapy (26,27) in our patients.

In conclusion, fusobacterial infection accounted for 6% of patients with single-pathogenic brain abscess. This study also shows that 64% of fusobacterial brain abscesses were monomicrobial infections. All infections were spontaneous and responded well to a combination of surgical intervention and antibiotic therapy. In this study, penicillin and chloramphenicol remained the choice of antibiotics in treatment. The prognosis is favorable with early diagnosis, relatively preserved consciousness on admission, and prompt treatment.

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