

A Case of Behçet's Disease-associated Brain Abscess Caused by *Veillonella*, Isolated as the Sole Pathogen by Culture of Aspirated Pus Discharge

Hidemasa NAGAI, Daikei TAKADA, Yasuhiko AKIYAMA and Kouzo MORITAKE

Department of Neurosurgery, Shimane University Faculty of Medicine, Izumo 693-850, Japan

(Received June 28, 2010; Accepted; August 27, 2010)

We present a case of *Veillonella* brain abscess associated with Behçet's disease. A review of the English literature revealed no reports of any similar cases. The patient was a 62-year-old man who had been treated for Behçet's disease for 20 years, and presented with right hemiparesis. MRI revealed a lesion with ring enhancement in the left motor area, and an open biopsy was performed. Culture of the aspirated purulent material revealed *Veillonella* spp. The patient was treated successfully with penicillin, and has since shown no recurrence. We discuss the relationship of *Veillonella* brain abscess to Behçet's disease with reference to dental caries and an immunosuppressed state.

Key words: Behçet's disease, brain abscess, dental caries, immunosuppression, *Veillonella* infection

INTRODUCTION

Veillonella species are anaerobic, non-motile, non-sporulating gram-negative cocci belonging to the family Neisseriaceae. The organisms appear in pairs, short chains, or irregular masses, and utilize pyruvate and lactate for metabolic energy. The most common species isolated from humans are *V. parvula*, *V. atypica* and *V. dispar*. *Veillonella* is usually part of the normal flora in the oral cavity, intestinal tract, and female genital tract, and has been considered to have low pathogenicity. When isolated from clinical specimens, the bacterium usually occurs in association with other aerobic or anaerobic organisms. On the other hand, *Veillonella*

has been reported as a pathogen in cases of chronic sinusitis (1), endocarditis (2-8), lung abscess (9), osteomyelitis (10, 11), myositis (12), bacteremia (13-16), and meningitis (17-19), sometimes being isolated as a single pathogen from specimen cultures. We reviewed the extensive literature related to infections from which *Veillonella* has been isolated in specimen cultures, but there has been no previous case report of a brain abscess in which *Veillonella* was the sole pathogen.

Here we report a rare case of *Veillonella* spp. isolated as the sole pathogen by culture from a brain abscess associated with Behçet's disease (BD). *Veillonella* is a rare causative pathogen of brain abscess, and there have been only two reports of brain abscess associated with BD among those related to host immunosuppression (20, 21). This is the first case report of *Veillonella* brain abscess associated with Behçet's disease. Here we discuss the relationship of *Veillonella* brain abscess to BD with reference to dental caries and the immunosuppressed state in the present patient.

PATIENTS AND METHODS

The patient was a 62-year-old man with a 20-year history of BD, who had been treated with the anti-inflammatory agent colchicine (1.0 mg/day p.o). His oral and genital ulcerations had been well controlled, and he had not been suffering from uveitis for a long period. He presented at the Department of Internal Medicine of our hospital complaining of right-sided muscle weakness. On physical examination, the patient was alert, with a body temperature of 36.2°C. Right hemiparesis (upper limb 3/5 and lower limb 4/5) was evident, and meningeal sign was absent. Initial laboratory tests revealed a white blood cell count of 7560/mm³, with 78% neutrophils,

Correspondence: Hidemasa Nagai, Enya 89-1, Izumo city, Shimane 693-8501, Japan

Tel: +81-853-202245

Fax: +81-853-218954

Email: h-nagai@med.shimane-u.ac.jp

1.1% eosinophils, 0.4% basophils, 16.1% lymphocytes, and 4.4% monocytes. The plasma concentration of C-reactive protein was 0.4 mg/dl, and the erythrocyte sedimentation rate was 7 mm/h. Magnetic resonance imaging (MRI) showed that the left motor cortex had low intensity in T1WI, was iso-intense in T2WI, and had high intensity in diffusion-weighted images (Fig. 1). Analysis of a lumbar puncture sample yielded the following values: cerebrospinal fluid (CSF) glucose = 66 mg/dl, CSF protein = 39 mg/dl, and cell count = $5/\text{mm}^3$ (75% lymphocytes and 25% neutrophils). Blood culture and CSF culture were negative. As the patient had shown acute onset of hemiparesis and had no evidence of local or systemic infection, he was treated with argatoroban and then methylprednisolone at 1000 mg/day under a diagnosis of cerebral infar-

tion or NeuroBehçet. MRI examination 3 days after admission demonstrated a lesion with ring enhancement that was suspected to be a malignant brain tumor or brain abscess (Fig. 2a). The patient was referred to our department and treated empirically with panipenem/betamipron (PAPM/BP) 2 g/day, followed by cefotaxim (CTX) 8 g/day + vancomycin (VCM) 2 g/day intravenously. Ten days later, his right hemiparesis had worsened and the brain lesion had become larger (Fig. 2b). He was therefore transferred to our department for histological diagnosis. Cerebral angiography revealed no tumor stain, and MR spectrography revealed a high peak of lactate, and low peaks of choline and creatinine. Vancomycin was discontinued, and CTX was changed to cefpirome (CPR) 4 g/day intravenously. We performed open craniotomy to obtain histologi-

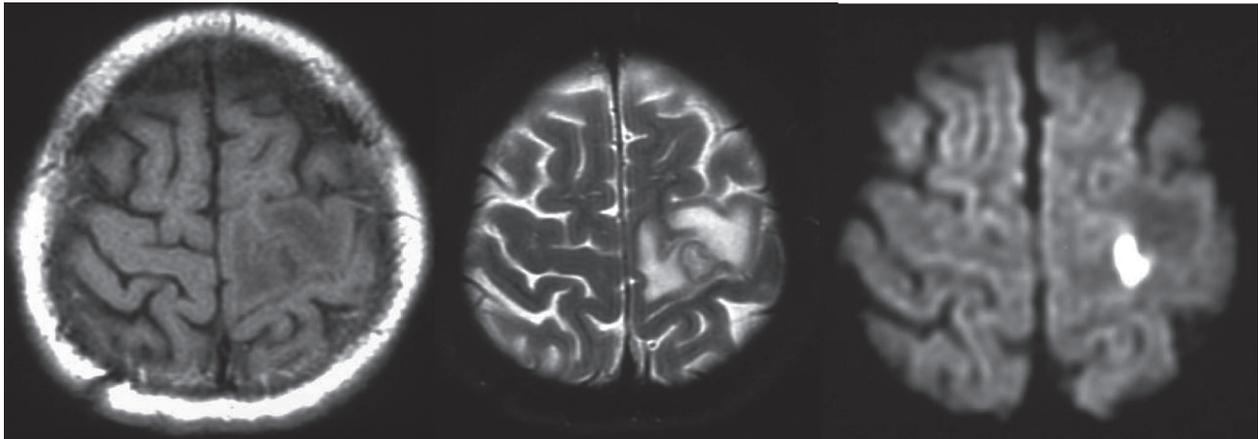


Fig. 1 MRI on admission, revealing low intensity in the T1WI (left), iso-intensity in the T2WI (middle), and high intensity in the diffusion-weighted image in the left motor cortex (right).

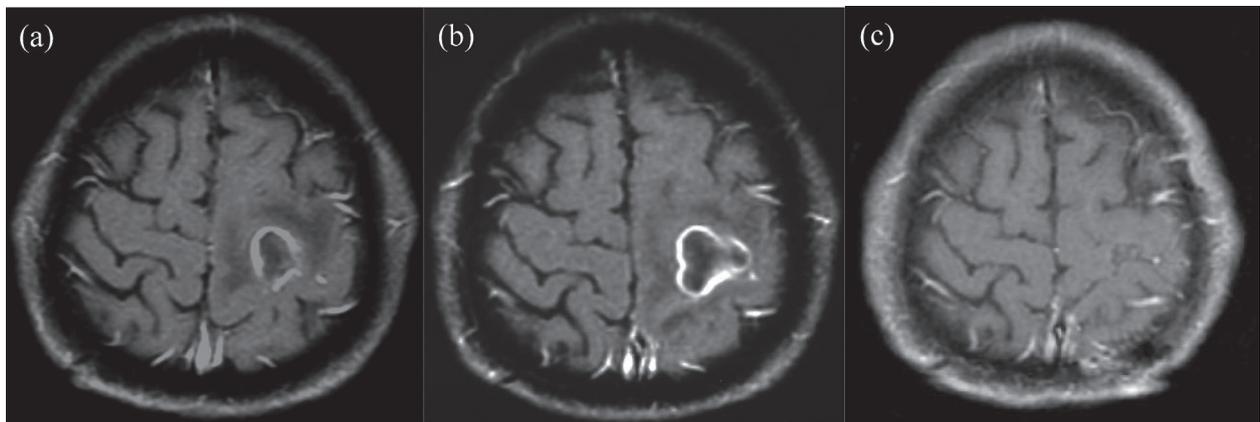


Fig. 2 Enhanced MRI, revealing serial changes at 3 days, 10 days and 9 weeks. (a) Enhanced MRI three days after admission shows a lesion with ring enhancement. (b) The lesion shows enlargement 10 days later. (c) MRI on the last day of penicillin therapy shows diminution of the lesion.

cal confirmation and allow bacteriological sampling. Intraoperative observation demonstrated spread of pus to the subdural space, indicating that the abscess wall had ruptured or was incomplete. We obtained about 1.0 ml of pus by echo-guided puncture and aspiration, and culture revealed *Veillonella* spp. The antimicrobial therapy was changed from CPR to ampicillin(ABPC)2 g/day, then to piperacillin(PIPC) 4 g/day, and subsequently to ampicillin/sulfamicillin (ABPC/ST) 6 g/day intravenously. Moreover, intravenous immunoglobulin (IVIG: 2.5 g/day*5 days) was administered twice a month. Since *Veillonella* is seldom cultured from brain specimens, we performed ⁶⁷Ga scintigraphy for further examination of the bacterial focus and detected dental caries. Culture of the dental caries yielded not *Veillonella* spp., but *Streptococcus anginosus*, *Enterobacter cloacae*, and *Prevotella loescheii*. We were unable to find any other source of infection. The patient also received penicillin for 9 weeks. MRI scan on the last day of penicillin therapy (oral amoxicillin 750 mg/day) showed only a small residual scar in the left frontal lobe (Fig. 2c). The patient has been followed up for 12 months since antibiotic withdrawal, and has shown no relapse.

DISCUSSION

1. *Veillonella* infection

Veillonella species are often regarded as commensal, and isolated together with other bacteria. On tooth surfaces, *Veillonella* colonization precedes the formation of more complex dental biofilms (22). Hughes *et al.* indicated that *V. atypica* and *V. dispar* predominate on the tongue, whereas *V. parvula* is markedly more numerous than the other two species in subgingival plaque (23). As entry of oral *Veillonella* into the bloodstream has been thought to be one source of bacteremia (22), if this bacterium reaches the blood circulation, it may spread hematogenously throughout the body, including the brain (10). However, *Veillonella* infection is not common. Martin reported that *Veillonella* spp. was isolated from only 1.0% (112 cases) of a total of 10,998 anaerobic bacterial cultures over a 2-year period (24). Therefore we investigated the well-documented English-language literature related to cases from which *Veillonella* had been isolated as the solitary pathogen (Table 1). In 15 cases, the mean patient age was 46.4±22.4 years, the female/male ratio was 6:9, and the mean body temperature

Table 1. Review of 15 cases of sole *Veillonella* infection from the available literature.

Case No.	Author, et al. Published year	Age	Sex	Diagnosis	V.species	BT (°C)	WBC (/mm ³)	CRP (mg/dl)	ESR (mm/hr)	Blood culture	Predisposing factor	Antibiotics
1	Loewe, 1946	35	M	endocarditis	<i>V.alcalescens</i>	38	7100	nd	92	+	dental caries	PC, PAH, sulfonamide
2	Greaves,1984	60	M	endocarditis	<i>V.alcalescens</i>	37.6	nd	nd	nd	-	congestive heart disease	DOXY, CEPR+GM, oral PCV
3	Atrosagaray, 1987	62	M	sepsis	<i>V.parvula</i>	38.5	14600	nd	nd	+	compromised host	GM, oral AMPC
4	Nukina, 1989	3	F	meningitis	<i>V.parvula</i>	40	29800	10.6	86	nd	blunt trauma, toothbrush	AMPC+MCIPC+CTX, FOM, CP
5	Loughrey, 1990	57	F	endocarditis	<i>V.dispar</i>	38	11500	6.1	nd	+	prosthetic mitral valve, periodontal disease	ABPC, M, CLDM
6	Singh, 1992	61	F	osteomyelitis	<i>V.parvula</i>	38.7	nd	nd	74	+	immunodeficiency	CTRX
7	Zussa, 1994	51	M	endocarditis	<i>V.alcalescens</i>	37.6	nd	nd	nd	+	prosthetic mitral valve	PCG
8	Beumont, 1995	47	F	myositis	<i>V.spp</i>	38.9	nd	nd	nd	+	immunodeficiency, compromised host	M
9	Fisher, 1996	5	M	sepsis	<i>V.parvula</i>	40	2500	nd	nd	nd	immunodeficiency, solid tumor	CTRX+CLDM
10	Houston, 1997	56	M	endocarditis	<i>V.dispar</i>	febrile	nd	nd	nd	+	prosthetic mitral valve	PC
11	Bhatti, 2000	47	F	meningitis	<i>V.parvula</i>	38.9	nd	nd	nd	+	chronic sinusitis	M+CTRX
12	Bongaerts, 2004	74	M	osteomyelitis	<i>V.parvula</i>	no	nd	6.8	47	nd	malnutrition, dental caries	PCG
13	Boo, 2005	49	M	endocarditis	<i>V.parvula</i>	38.3	30800	nd	nd	-	prosthetic mitral valve, periodontal disease	M
14	Rovero, 2005	75	F	endocarditis	<i>V.montpellierensis</i>	febrile	nd	nd	nd	nd	diabetes	AMPC+GM
15	Strach, 2006	17	M	sepsis	<i>V.parvula</i>	40	17000	nd	nd	+	immunodeficiency	DOXY

The table summarizes author & publication year, patient age, sex, diagnosis, *Veillonella* species, body temperature, WBC, CRP, ESR, blood culture, predisposing factors, and antibiotics. The abbreviations listed as below are CLDM: clindamycin, CP: chloramphenicol, GM: gentamicin, DOXY: doxycycline hydrochloride, M: metronidazole, PC: penicillin, PCG: benzylpenicillin, PCV: phenoxymethylpenicillin, MCIPC: cloxacillin, ABPC: ampicillin, AMPC: amoxicillin, FOM: fosfomicin, CEPR: cefapirin, CTX: cefotaxim, CTRX: ceftriaxone, PAH: para-aminohippurate, V: *Veillonella*, and nd: not described.

was $38.7 \pm 0.9^\circ\text{C}$. The median peripheral leukocyte count was $14600/\text{mm}^3$. The *Veillonella* infections were diagnosed as endocarditis [7], osteomyelitis [2], sepsis/bacteremia [3], myositis [1], and meningitis [2]. The species of *Veillonella* cultured from these cases were *V. parvula* [8], *V. atypica* [0], *V. dispar* [2], *V. alcalescens* [3], *Veillonella* spp. [1], and *V. montpellierensis* [1]. Positive blood culture was observed in 9 cases. The underlying conditions predisposing to infection with this organism were dental disease [5], diabetes [1], prosthetic valve [4], chronic sinusitis [1], heart disease [1], solid tumor [1], malnutrition [1], compromised hosts [2], and immunodeficiency [4]. The cases summarized in Table 1 suggest that immunosuppression can play a major role in the pathogenesis of the infection.

To our knowledge, there has been no previous case report of a brain abscess in which *Veillonella* was the sole pathogen. However, there have been two reports of brain abscess in which *Veillonella* was a component of polymicrobial infection. Brook reported a 62-year-old man with a right frontal brain abscess associated with periodontal abscess, in which *V. parvula* was isolated together with *Fusobacterium nucleatum*, *Prevotella melangingenica*, and *Peptostreptococcus magnus* from the brain abscess (25). Heineman *et al.* reported three cases of brain abscess including *Veillonella* spp. in their observations of 18 cases (26). The patients were a 20-year-old man with a right temporal brain abscess associated with chronic otitis media, a 22-year-old man with a left temporal and parietal brain abscess associated with chronic otitis media, and a 32-year-old man with a left frontal brain abscess associated with acute tonsillitis. These cases were caused by multiple pathogens via sinus infection.

2. Relationship between BD and brain abscess

Although the source of *Veillonella* in the present case was unknown, we speculated that the brain abscess was secondary to chronic inflammation of the oral mucosa, which could have been associated with BD. In fact the patient had a history of gingival disease lasting several years and had untreated dental caries that harbored *Streptococcus anginosus*, *Enterobacter cloacae* and *Prevotella loescheii*, but not *Veillonella*, probably as a result of oral mi-

crobial substitution after long-term antibiotic drug therapy.

A search of the literature related to *Veillonella* infection suggested that immunosuppression could play a major role in the pathogenesis of the infection (12, 15). Coincidentally, the previous cases of brain abscess associated with BD were reportedly related to the use of immunosuppressant drugs (20, 21). It was naturally assumed that the patient was in an immunosuppressed state for some reason. Generally, oral bacterial infection in patients with BD characterized by recurrent aphthous stomatitis is considered to be suppressed because of the high immunoglobulin A (IgA) level derived from a hyperactive state of the common mucosal immune system in BD. However, we speculate that if the secretory IgA level had been reduced by some form of stress, mucosal immunity would have broken down, as indicated in reports of *Veillonella* infection that might have been related to secretory IgA deficiency (11, 16). Moreover, if a BD patient such as the present one receives long-term treatment with a drug such as colchicine, which inhibits neutrophil motility and activity, the protective mechanism of the mucous membrane could easily deteriorate, finally leading to spread of the oral bacterium from the blood circulation to the brain.

3. Treatment for *Veillonella* brain abscess

Penicillin has generally been the antibiotic agent of choice for treatment of *Veillonella* infections. Other β -lactams, metronidazole and clindamycin, have also been used. *Veillonella* is resistant to VCM, aminoglycosides, ciprofloxacin, and tetracycline, and is slightly responsive to erythromycin. Cephalosporins and carbapenems seem to be effective for *Veillonella* infections, at least on the basis of a review of the available data. However, panipenem/betamipron (PAPM/BP), cefotaxime (CTX), and cefpirome (CPR) were clinically less active against *Veillonella* brain abscess in the present case. *Veillonella* isolated from infections in medically compromised patients is reported to be penicillin-resistant (22). Although the resistance mechanism in *Veillonella* is unknown, alternative agents for penicillin-resistant *Veillonella* strains are thought to be clindamycin, chloramphenicol, and metronidazole.

Fass *et al.* stated that clindamycin should be considered as a primary antibiotic for the treatment of anaerobic infections (14). On the other hand, Chow *et al.* has reported that clindamycin does not appear to cross the blood-brain barrier and therefore should not be used in cases of suspected meningitis (27). Nukina *et al.* have reported that chloramphenicol is highly effective for CNS infections because of its easy penetration into the CSF, and that surgical treatment, including drainage of the abscess, is important (19). However, as chloramphenicol can have a rare but severe hematological side effect, its use is not always advisable. Metronidazole, which is widely used for treating infections due to *Trichomonas vaginalis*, has been used for anaerobic *Veillonella* infection. This drug has been shown to exert rapid and consistent bactericidal activity against many strictly anaerobic bacteria, because it diffuses at high concentrations into all body tissues including the CNS (28). The results of our treatment strategy indicate that metronidazole could be a suitable second choice for *Veillonella* brain abscess.

In conclusion, we have reported a rare case of *Veillonella* brain abscess associated with Behçet's disease. The organism was isolated singly in pure culture from the affected patient, and successful treatment was achieved with penicillin over a period of 9 weeks.

ACKNOWLEDGMENTS

We thank Mitsuhiro Daisu, Keiji Sugimoto, Takeshi Miyazaki and Takashi Shingu, Department of Neurosurgery, Shimane University Faculty of Medicine, for their support.

REFERENCES

- 1) Su WY, Liu C, Hung SY and Tsai WF (1983) Bacteriological study in chronic maxillary sinusitis. *Laryngoscope* 93: 931-934.
- 2) Boo TW, Cryan B, O'Donnell A and Fahy G (2005) Prosthetic valve endocarditis caused by *Veillonella parvula*. *J Infect* 50: 81-83.
- 3) Greaves WL and Kaiser AB (1984) Endocarditis due to *Veillonella alcalescens*. *South Med J* 77: 1211-1212.
- 4) Houston SD, Taylor D and Rennie R (1997) Prosthetic valve endocarditis due to *Veillonella dispar*: successful medical treatment following penicillin desensitization. *Clin Infect Dis* 24: 1013-1014.
- 5) Loewe L, Rosenblatt P and Altire-Werber E (1946) A refractory case of subacute bacterial endocarditis due to *Veillonella gazogenes* clinically arrested by a combination of penicillin, sodium para-aminohippurate, and heparin. *Am Heart J* 32: 327-338.
- 6) Loughrey AC and Chew EW (1990) Endocarditis caused by *Veillonella dispar*. *J Infect* 21: 319-321.
- 7) Rovey C, Etienne A, Foucault C, Berger P and Brouqui P (2005) *Veillonella montpellierensis* endocarditis. *Emerging Infect Dis* 11: 1112-1114.
- 8) Zussa C, Ius P, Cesari F, Valfré C, Totis O, Canova C and Pugina P (1994) Fortuitous detection of prosthetic valve endocarditis caused by an uncommon etiologic agent. *J Thorac Cardiovasc Surg* 107: 1167-1168.
- 9) Mori T, Ebe T, Takahashi M, Isonuma H, Ikemoto H and Oguri T (1993) Lung abscess: analysis of 66 cases from 1979 to 1991. *Intern Med* 32: 278-284.
- 10) Bongaerts GP, Schreurs BW, Lunel FV, Lemmens JA, Pruszczynski M and Merckx MA (2004) Was isolation of *Veillonella* from spinal osteomyelitis possible due to poor tissue perfusion? *Med Hypotheses* 63: 659-661.
- 11) Singh N and Yu VL (1992) Osteomyelitis due to *Veillonella parvula*: case report and review. *Clin Infect Dis* 14: 361-363.
- 12) Beumont MG, Duncan J, Mitchell SD, Esterhai JL Jr. and Edelstein PH (1995) *Veillonella* myositis in an immunocompromised patient. *Clin Infect Dis* 21: 678-679.
- 13) Arrosagaray PM, Salas C, Morales M, Correas M, Barros JM and Cordon ML (1987) Bilateral abscessed orchiepididymitis associated with sepsis caused by *Veillonella* and *Clostridium perfringens*: case report and review of the literature. *J Clin Microbiol* 25: 1579-1580.
- 14) Fass RJ, Scholand JF, Hodges GR and Saslaw S (1973) Clindamycin in the treatment of serious anaerobic infections. *Ann Intern Med* 78: 853-859.

- 15) Fisher RG and Denison MR (1996) *Veillonella parvula* bacteremia without an underlying source. *J Clin Microbiol* 34: 3235-3236.
- 16) Strach M, Siedlar M, Kowalczyk D, Zembala M and Grodzicki T (2006) Sepsis caused by *Veillonella parvula* infection in a 17-year-old patient with X-linked agammaglobulinemia (Bruton's disease). *J Clin Microbiol* 44: 2655-2656.
- 17) Bhatti MA and Frank MO (2000) *Veillonella parvula* meningitis: case report and review of *Veillonella* infections. *Clin Infect Dis* 31: 839-840.
- 18) Borowsky AD, Stein SM, Tulipan NB and Dermody TS (1995) Meningitis caused by mixed anaerobic species complicating tethered cord syndrome. *Clin Infect Dis* 21: 706-707 (Letter).
- 19) Nukina S, Hibi A and Nishida K (1989) Bacterial meningitis caused by *Veillonella parvula*. *Acta Paediatr Jpn* 31: 609-614.
- 20) Ganau S, Berenguer J, Pujol T and Mercader JM (2001) An unusual central nervous system manifestation of Behçet's disease. *Am J Roentgenol* 177: 721-722.
- 21) Ho CL and Deruytter MJ (2005) Manifestations of Neuro-Behçet's disease. Report of two cases and review of the literature. *Clin Neurol Neurosurg* 107: 310-314.
- 22) Nyfors S, Kononen E, Bryk A, Syrjanen R and Jousimies-Somer H (2003) Age-related frequency of penicillin resistance of oral *Veillonella*. *Diagn Microbiol Infect Dis* 46: 279-283.
- 23) Hughes CV, Kolenbrander PE, Andersen RN and Moore LV (1988) Coaggregation properties of human oral *Veillonella* spp.: relationship to colonization site and oral ecology. *Appl Environ Microbiol* 54: 1957-1963.
- 24) Martin WJ (1974) Isolation and identification of anaerobic bacteria in the clinical laboratory. A 2-year experience. *Mayo Clin Proc* 49: 300-308.
- 25) Brook I (2006) Microbiology of intracranial abscesses associated with sinusitis of odontogenic origin. *Ann Otol Rhinol Laryngol* 115: 917-920.
- 26) Heineman HS and Braude AI (1963) Anaerobic infection of the brain. Observations on eighteen consecutive cases of brain abscess. *Am J Med* 35: 682-697.
- 27) Chow AW, Leake RD, Yamauchi T, Anthony BF and Guze LB (1974) The significance of anaerobes in neonatal bacteremia: analysis of 23 cases and review of the literature. *Pediatrics* 54: 736-745.
- 28) Warner JF, Perkins RL and Cordero L (1979) Metronidazole therapy of anaerobic bacteremia, meningitis, and brain abscess. *Arch Intern Med* 139: 167-169.