Cavernous Sinus Thrombosis and Cerebral Infarction Caused by *Fusobacterium nucleatum* Infection

Chen-Sheng Chang, MD; Chia-Wei Liou[1], MD; Chin-Chang Huang[2], MD; Chun-Chung Lui[3], MD; Ku-Chou Chang[1], MD

We report an unusual case of fusobacterial infection with secondary intracranial invasion. The condition was complicated by a cavernous sinus thrombosis and ischemic stroke. The patient was a 63-year-old woman with no history of systemic disease who had undergone a tooth extraction before the onset of symptoms. She initially suffered from sphenomaxillary sinusitis and a cavernous sinus thrombosis, and subsequently developed meningitis. Cerebrospinal fluid examination suggested a pyogenic infection. Anaerobic culture revealed *Fusobacterium nucleatum*. However, despite immediate antibiotic therapy, her condition remained unstable over the next few days, and she eventually developed an ischemic stroke. We describe our experience in the management of this case of anaerobic meningitis and the unusual complication of ischemic stroke; this case suggests that more aggressive therapy in addition to empirical antibiotics may be warranted. *(Chang Gung Med J 2004; 27:459-63)*

Key words: **cerebral infarction, etiology, infection, *Fusobacterium nucleatum*, cavernous sinus thrombosis.**

Fusobacterium nucleatum is a strictly anaerobic gram-negative rod bacterium normally found in the oral cavity, and in the urogenital, gastrointestinal, and upper respiratory tracts. This organism is not a pathogen of these tracts under normal conditions.[1] However, in patients predisposed to infection or who are immunocompromised, it may act as an infectious pathogen causing clinical syndromes such as central nervous system infection including brain abscess.[2-4] The routes of infection are thought to be via an adjacent extracranial infection or through hematogeneous spread from a remote focus. We report a case of fusobacterial meningitis caused by the *F. nucleatum* with complications, specifically a cavernous sinus thrombosis and ischemic stroke. There have been a few pediatric cases complicated by another species, *F. necrophorum*, with a similar presentation.[5-8]

CASE REPORT

A 63-year-old woman was hospitalized in July 1998 because of a persistent high fever combined with right eye congestion, proptosis, and eye pain. She had been quite healthy until about 3 weeks prior to the admission when she began to suffer from right frontal headaches, puffiness of the right eye, and fever. These symptoms all developed following a tooth extraction. Three days before admission, diplopia and high fever developed. The fever persisted and consciousness gradually deteriorated. Upon losing consciousness, she was admitted to our hospital. Physical examination in the emergency department revealed right-eye ptosis with limitation of eyeball movement. Her neck was stiff with positive meningeal signs. Muscle strength and sensation were

From the Department of Neurology, E-Da Hospital, I-Shou University; [1]Department of Neurology, Chang Gung Memorial Hospital, Kaoshiung; [2]Department of Neurology, Chang Gung Memorial Hospital, Taipei; [3]Department of Neuroradiology, Chang Gung Memorial Hospital, Kaohsiung; Chang Gung University, Taoyuan.
Received: Mar. 5, 2003; Accepted: Sep. 1, 2003
Address for reprints: Dr. Chia-Wei Liou, Department of Neurology, Chang Gung Memorial Hospital. 123, Dabi Road, Niaosung Shiang, Kaohsiung, Taiwan 833, R.O.C. Tel.: 886-7-7317123 ext. 2285; Fax: 886-7-7318762; E-mail: cwliou@ms22.hinet.net

symmetrically responsive to pain stimulation. Routine blood examination revealed leucocytosis (19.8×10^9/L) with a high neutrophil count (65%) but normal biochemical and electrolyte data. A cerebral computed tomographic (CT) scan showed cloudiness over the left maxillary and sphenoid sinuses. Post-contrast medium injection disclosed a filling defect in the cavernous sinus and an engorged superior ophthalmic vein on the right side. Erosion of the left lateral sphenoid sinus wall was also noted (Fig. 1). Under a tentative diagnosis of cavernous sinus lesion and meningitis, a cerebrospinal fluid (CSF) study was performed. The data showed pleocytosis (105/mm^3) with a high neutrophil count (55%), elevated lactate (38.5 mg/dl; normal: 20-30 mg/dl) and protein levels (78 mg/dl; normal: 20-40 mg/dl), and a depressed glucose level (38 mg%), while the blood sugar was 88 mg%. Antibiotic therapy with penicillin and chloramphenicol was begun, and then changed to latamoxef immediately after a diagnosis of bacterial meningitis of unknown nature was made. A biopsy from the sphenoid sinus was performed to rule out the possibility of fungal infection. Her clinical condition improved considerably, and she became alert after the antibiotic therapy was begun. However, she had a sudden episode of slurred speech and mild right limb weakness 5 days after admission. A brain magnetic resonance image (MRI) disclosed abnormal enhancement of the basal cistern and left Sylvian fissure, as well as a focal ischemic change over the left temporal region and the left basal ganglion (Fig. 2). A series of studies looking for underlying cardiac disease and other risk factors for stroke included cardiac echography and laboratory examinations such as fluorescent treponemal antibody with absorption test, prothrombin time, antithrombin factor, and antiphospholipid antibody. All produced negative results. CSF culture demonstrated an anaerobic organism, which was identified as *Fusobacterium nucleatum*. Drug-sensitivity testing revealed that this microorganism was sensitive to penicillin, chloramphenicol, piperacillin, latamoxef, and metronidazole. Treatment with latamoxef was continued for 20 days. Unfortunately, a recurrence of severe right limb weakness and dysarthria was noted. A follow-up MRI showed improvement in the enhancement of the left Sylvian fissure and a return to normal size of the right superior ophthalmic vein. However, an enlarged ischemic zone over the left

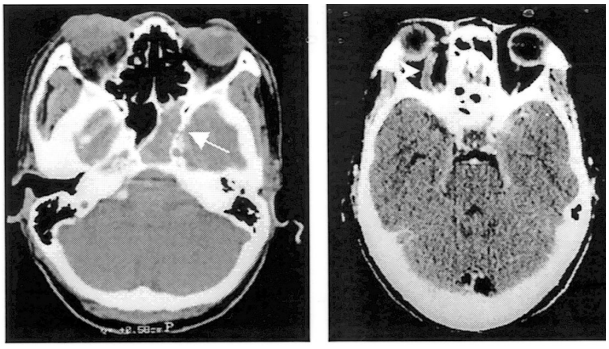

Fig. 1 Brain CT revealing cloudiness over the left sphenoid sinus and an engorged superior ophthalmic vein on the right side (arrowheads). Erosion of the lateral sphenoid sinus wall can be noted on the left side (arrow).

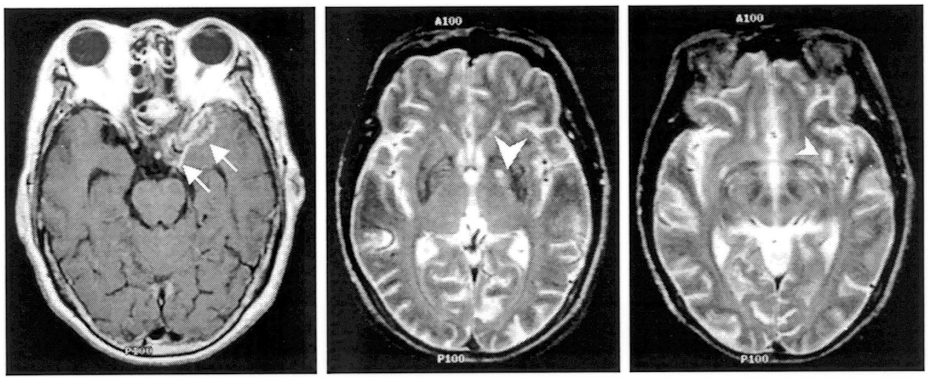

Fig. 2 Brain MRI showing an abnormal enhancement in the basal cistern and left Sylvian fissure on the left side (arrows), as well as a focal ischemic change over the left temporal region and basal ganglion (arrowheads).

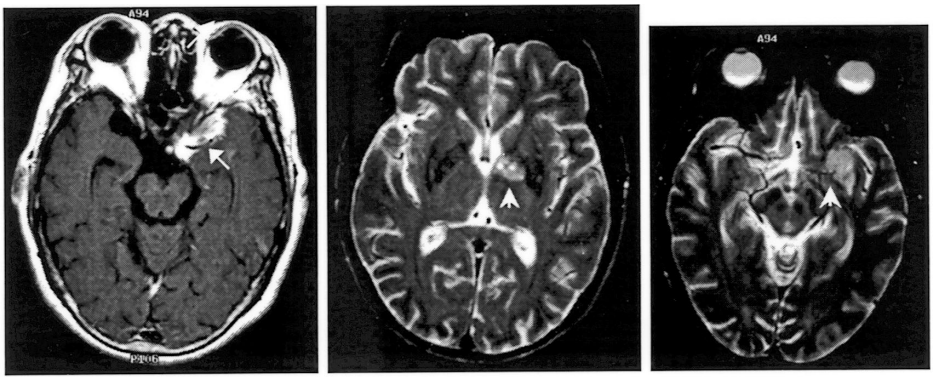

Fig. 3 Twenty days after first MRI scan, follow-up MRI showing a stationary change in the enhancement of the left Sylvian fissure and an infarct in the left basal ganglion (arrows). In addition, progressive change in the ischemic lesion over the left temporal and the basal ganglion can be noted (arrowheads).

temporal lobe and basal ganglion was found (Fig. 3). The antibiotic regimen was maintained, and antiplatelet agents were added. Fluctuations in the right hemiparesis were noted during the following 3 days. Her condition stabilized after administration of steroids. A follow-up CSF test was essentially normal 1 month later. She was discharged 2 months after admission, but the left-side hemiplegia still remained 6 months after discharge.

DISCUSSION

This patient had an unusual fusobacterial infection that involved the sphenomaxillary sinus, cavernous sinus, and meninges. She subsequently developed an acute cerebral infarction despite empirical antibiotic therapy. A brain MRI demonstrated that the infarction was located close to the circumscribed region of this infection and had a time of onset in sequence with the spread of the infection. It is therefore reasonable to suggest that the infection either directly or indirectly induced the cerebral infarction through its effect on the intracranial vessels. Central nervous system (CNS) infection has been suggested as a common cause of cerebral infarction.[9] Tuberculous meningitis, neurosyphilis, rhinocerebral mucormycosis, and other infections have all been reported, and vasculitis which involves the corresponding vessels has been suggested as the probable pathogenesis.[9] The CNS infection in our patient appeared to be responsible for the complication of the stroke. This rare condition has only been reported in a limited number of patients who had a fusobacterial CNS infection caused by a different species of F. necrophorum;[5-8] a preexisting oropharyngeal infection was suggested as the underlying etiology in those cases. In our patient, the recent tooth extraction appeared to be the route of infection. Therefore, clinicians should be aware of this type of complication.

Progressive intracranial invasion from an extracranial focus is unusual in patients with a fusobacterial infection. As a result, our patient was initially diagnosed with mucormycosis infection due to similarities in the clinical presentation.[10] The pathogenesis for this unusual course was elucidated using serial brain imaging studies. The bony defect located near the infectious focus appeared to be the point of entry. From there, the pathogens invaded and extended intracranially to the Sylvian fissure and basal cistern. Engorgement of the superior ophthalmic vein and partial obliteration of the cavernous sinus are reasonable explanations for the subsequent generation of eye signs. In addition, lesions in the left temporal and basal ganglion regions suggestive of a focal ischemic change were noted on admission. Progressive ischemic change despite antibiotic therapy eventually resulted in the focal cerebral infarction.

Almost all patients with fusobacterial infections have a benign clinical course providing that an effective antimicrobial therapy can be given without delay.[11,12] However, severe complications developed in our patient despite empirical administration of antibiotics. Delays in the beginning of antibiotic

therapy after early onset of cavernous sinus thrombosis symptoms may be a critical turning point. Moreover, unusual complications of vasculitis and its related cerebral infarction required more than the common therapeutic regimen for such an infection. Thus, the efficacy of empirical antibiotics as a therapeutic mainstay should be reconsidered. A combination of antiplatelet, anticoagulant, or even steroid therapy may be used to prevent such delayed complications. In conclusion, *Fusobacterium nucleatum* infection can cause intracranial invasion and serial intracranial complications including acute cerebral infarction. The pathogenesis appears to be similar to that for other organisms. However, the characteristics of the delayed and progressive onset of complications in this case, despite empirical antibiotic therapy, are poorly understood and thus may warrant more-aggressive therapeutic modalities in future cases like this.

REFERENCES

1. Lancaster LA, Attebery HR. Fusobacteria. In: Braude AI, Davis CE, Fierer J, eds. Infections disease and medical microbiology. Philadelphia: WB Saunders, 1986:421-5.
2. Swartz MN. Central Nervous System Infection. In: Finegold SM, George WL, eds. Anaerobic Infections in Humans. San Diego: Academic Press, 1989:156-87.
3. Taguchi Y, Sato J, Nakamura N. Gas-containing brain abscess due to *Fusobacterium nucleatum*. Surg Neurol 1981;16:408-10.
4. Saez-Llorens XJ, Umana MA, Odio CM, McCracken GH Jr, Nelson JD. Brain abscess in infants and children. Pediatr Infect Dis J 1989;8:449-58.
5. Spencer CH, Slusher CW, Sanders CV, Aldridge KE. *Fusobacterium necrophorum* sepsis with cerebral infarction. South Med J 1989;82:1040-3.
6. Jones TH, Bergvall V, Bradshaw JPP. Carotid artery stenoses and thrombosis secondary to cavernous sinus thromboses in *Fusobacterium necrophorum* meningitis. Postgrad Med J 1990;66:747-50.
7. Bader-Meunier B, Pinto G, Tardieu M, Pariente D, Bobin S, Dommergues JP. Mastoiditis, meningitis and venous sinus thrombosis caused by *Fusobacterium necrophorum*. Eur J Pediatr 1994;153:339-41.
8. Larsen PD, Chartrand SA, Adickes ED. *Fusobacterium necrophorum* meningitis associated with cerebral vessel thrombosis. Pediatr Infect Dis J 1997;16:330-1.
9. Dalal PM, Dalal KP. Cerebrovascular manifestations of infectious disease. In: Vinken PJ, Bruyn GW, Klawans HL, et al, eds. Handbook of clinical neurology, Vol II. "Vascular Disease" Part III. Washington: Elsevier Science Publishers, 1989:411-41.
10. Lowe JT, Hudson WR. Rhinocerebral phycomycosis and internal carotid artery thrombosis. Arch Otolaryngol 1975;101:100-3.
11. Finegold SM. Therapy of Anaerobic infections. In: Finegold SM, George WL, eds. Anaerobic infections in human. San Diego: Academic Press, 1989:799-814.
12. Appelbaum PC, Spangler SK, Jacob MR. Susceptibilities of 394 Bacteroides fragilis, non-B. fragilis group Bateroides species, and Fusobacterium species to newer antimicrobial agents. Antimicrob Agents Chemother 1991;35:1212-4.

*Fusobacterium nucleatum*菌感染後併發腦靜脈竇栓塞及腦梗塞

張振聲 劉嘉爲[1] 黃錦章[2] 呂鎮中[3] 張谷州[1]

本文報告一少見因fusobacterial感染合併續發性顱內侵襲之一病例。並且先後併發腦靜脈竇栓塞、腦膜炎及腦血管阻塞性中風，此感染中樞神經系統及其疾病過程甚爲罕見。該病例爲一63歲女性，於拔牙後數週內先後併發鼻竇炎、腦靜脈竇栓塞及腦膜炎。腦脊髓液檢查顯示爲化膿性細菌感染；厭氧性微生物培養發現爲*Fusobacterium nucleatum*菌。雖病人自就醫初始即給予抗生素治療，然數日後仍併發腦血管梗塞。本文除敘述該患者疾病發生及其治療之過程，並建議除經驗抗生素治療外之積極治療。(長庚醫誌 2004;27:459-63)

關鍵字：腦梗塞，病因，感染，*Fusobacterium nucleatum*，腦靜脈竇栓塞。

義守大學　義大醫院　神經內科；[1]長庚紀念醫院　高雄院區　神經內科；[2]長庚紀念醫院　台北院區　神經內科；[3]長庚紀念醫院　高雄院區　放射診斷科

受文日期：民國92年3月5日；接受刊載：民國92年9月1日。

索取抽印本處：劉嘉爲醫師，長庚紀念醫院　神經內一科。高雄縣833鳥松鄉大埤路123號。Tel.: (07)7317123轉2285; Fax: (07)7318762; E-mail: cwliou@ms22.hinet.net