ASPERGILLOSIS OF THE CENTRAL NERVOUS SYSTEM: A CATASTROPHIC OPPORTUNISTIC INFECTION

Piya Pongbhaesaj, Charungthai Dejthevaporn, Supoch Tunlayadechanont, Rawiphan Witoonpanich, Somnuek Sungkanuparph and Asda Vibhagool

Division of Neurology and Division of Infectious Disease, Department of Medicine, Faculty of Medicine at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Abstract. The clinical features and outcome of the treatment of aspergillosis of the central nervous system (CNS) in Thai patients are presented. The patients who were diagnosed as having CNS aspergillosis by tissue biopsy or culture from January 1,1991 to December 31, 2000 were retrospectively reviewed. The study variables including age, sex, underlying disease, symptoms and signs, neuro-imaging studies, pathological findings and outcome of treatment, are described. There were seven cases of aspergillosis of the central nervous system. Four patients were male. The median age was 65 years (range 36-78 years). The most common underlying disease was diabetes mellitus (4/7; 57.1%). Two patients (28.6%) had no underlying disease. The most common primary site of infection was the paranasal sinuses (6/7; 85.7%). The most common clinical presentation was headache (6/7; 85.7%). Common neurological signs included multiple cranial nerve palsies (5/7; 71.4%) and alteration of consciousness (3/7; 42.9%). The median duration of the symptoms prior to admission was 60 days (range 8-180 days). All patients were treated with intravenous antifungal agents at high doses. Extensive surgery was performed in 6 patients. The mortality rate was very high (6/7; 85.7%). The median time from diagnosis and treatment to death was 53 days (22-720 days). Aspergillosis of the CNS should be considered in those with clinical features of headache, multiple cranial nerve palsies and alteration of consciousness accompanied by sinusitis, especially in elderly and diabetic patients. It remains a catastrophic opportunistic infection in spite of the current intensive and aggressive treatment.

INTRODUCTION

Invasive aspergillosis is a rare disease and remains a catastrophic condition with high morbidity and mortality. Aspergillosis of the central nervous system (CNS) is usually the worst manifestation of invasive aspergillosis, comprising about 10-20% of cases (Denning, 2000). The first case of aspergillosis involving the brain was reported by Oppe in 1897. In that case, aspergillosis started in the sphenoid sinus and extended to the optic chiasm and right internal carotid artery (Oppe, 1897). Very few cases of CNS aspergillosis were subsequently reported until the 1970s (Kim *et al*, 1993). Since then, there has been increasing incidence of CNS aspergillosis with the advent of more aggressive medical interventions which impair the immune response of the host.

It is now well known that this catastrophic infection frequently occurs in the setting of immunocompromised conditions such as leukemia, organ transplantations (Walsh *et al*, 1985; Pagano *et al*, 1996; Wald *et al*, 1997), diabetes mellitus (Torre-Cisneros *et al*, 1993), those receiving immunosuppressive drugs, chemotherapy or corticosteroids (Beal *et al*, 1982) and intravenous drug use (Walsh *et al*, 1985). Although aspergillosis can occur in immunocompetent hosts (Kim *et al*, 1993; Chandra *et al*, 2000), the incidence is very low. Sometimes it occurs as a complication of neurosurgery (Haran and Chandy, 1993; Kim *et al*, 1993; Darras-Joly *et al*, 1996; Sharma *et al*, 1997; Viriyavejakul *et al*, 1999). CNS aspergillosis is frequently caused by hematogenous dissemination from an extracerebral focus, direct extension from the paranasal sinuses or contamination during neurosurgical procedures. The mortality rate of this condition ranges from 75 to 100% (Young *et al*, 1970; Denning and Stevens, 1990) in spite of therapy with am-

Correspondence: Dr Rawiphan Witoonpanich, Division of Neurology, Department of Medicine, Ramathibodi Hospital, Rama 6 Road, Bangkok 10400, Thailand.
Tel: 66 (0) 2201 1386; Fax: 66 (0) 2246 2123
E-mail: rarwt@mahidol.ac.th

photericin B and surgery. Previously, there were only two reports of cerebral aspergillosis in Thai patients (Visudhiphan *et al*, 1973; Viriyavejakul *et al*, 1999). The scanty case reports might have partly been due to the lack of confirmation of the diagnosis. In this study, we report our experience of CNS aspergillosis in clinical presentation, laboratory and neuro-imaging findings and outcomes of treatment in Thai patients.

PATIENTS AND METHODS

Medical records of the patients who were definitely diagnosed as CNS aspergillosis in Faculty of Medicine at Ramathibodi Hospital, Mahidol University, between January 1, 1991 and December 31, 2000 were retrospectively reviewed. All patients who were diagnosed as having CNS aspergillosis and had histopathological documentation of tissue invasion by branched septate hyphae compatible with aspergillosis and/or positive cultures for *Aspergillus* were included. The study variables including age, sex, underlying disease, symptoms and signs, neuro-imaging studies, pathology and outcomes of treatment are described.

RESULTS

There were 7 cases of CNS aspergillosis. Four patients (57.1%) were male. Table 1 summarizes the clinical features in each patient. The median age was 65 years (range 36-78 years). Diabetes mellitus was the most common underlying disease and found in 4 patients (57.1%). Other underlying diseases were old cerebrovascular accident (CVA), hypertension and hematologic malignancy, one patient each (14.3%). Two patients (28.6%; case 2,7) had no underlying disease. There was only one patient (case 5) who had received immunosuppressive therapy before developing symptoms and signs of the infection. The most common primary site of infection was the paranasal sinuses (PNS) which was found in 6 patients (85.7%). Another patient (14.3%) developed pneumonia of the right upper lung which was probably the source of infection. Other organs which were involved, apart from the CNS, were paranasal sinuses in 6 (85.7%), eyes in 3 (42.9%) and lungs in 2 patients (28.6%). Lung involvement was found at autopsy in one patient (case 2).

Symptoms and signs of patients with CNS aspergillosis are summarized in Table 2. Headache was the most common clinical presentation, presenting in 6 out of 7 patients (85.7%). Other clinical presentations were multiple cranial nerve palsies (5/7; 71.4%), alteration of consciousness (3/7; 42.9%), visual loss (2/7; 28.6%), fever (2/7; 28.6%) and seizures (1/7; 14.3%). The affected cranial nerves were optic nerve (3/5; 60%), oculomoter nerve (3/5; 60%), trochlear nerve (3/5; 60%), trigeminal nerve (2/5; 40%), abducens nerve (3/5; 60%), facial nerve (1/5; 20%), vestibulocochlear nerve (1/5; 20%), glossopharyngeal nerve (2/5; 40%) and vagus nerve (2/5; 40%). The median duration of symptoms and signs prior to admission was 60 days (range 8-180 days). The median time taken to get the clinical diagnosis and treatment after admission was 8 days (range 5-30 days).

Aspergillus fumigatus was recovered from cultured specimens in 3 patients (42.9%). For others, there was evidence of branched septate hyphae suggestive of *Aspergillus* infection from biopsy. The specimens that yielded positive cultures were paranasal sinuses (5/7; 71.4%), brain tissue (4/7; 57.1%) and bronchoalveolar lavage (1/7; 14.3%). The PNS was the most common diagnostic biopsied specimen before death (5/7; 71.5%). Other specimens were from brain tissue (2/7; 28.6%), nasopharynx (1/7; 14.3%) and lung (1/7; 14.3%).

Other laboratory findings including CBC and sodium levels on admission are presented in Table 2. The median numbers of white blood cells, polymorphonuclear cells, hematocrit and platelet counts were 9,800/mm^3 (6,370-15,400), 74% (60-93%), 32.25% (24.6-42.9%) and 380,500/ mm^3 (311,000-684,000) respectively. On admission, two patients had hyponatremia caused by SIADH.

Magnetic resonance imaging (MRI) and computerized axial tomography (CT) of the brain were performed in 4 and 3 patients respectively. Multiple lesions with ring enhancement consistent with cerebral abscesses were demonstrated in 6 patients (85.7%) mostly in the temporal and frontal lobes. A single such lesion was seen in only one patient. Other cerebral findings were leptomeningeal enhancement (2/7; 28.6%), perilesional edema (2/7; 28.6%), hydrocephalus (2/7; 28.6%) and brain herniation (1/7; 14.3%). The most common site of an extracerebral lesion

Table 1
Clinical features of patients with CNS aspergillosis.

Patient No.	Age (y)/ sex	Underlying diseases	Immuno-suppressive therapy	Symptoms and signs	Primary site of infection	Other sites of aspergillosis	Culture positive specimens	Infecting aspergillus species	Diagnostic biopsy specimens
1	65/M	no	no	Headache, blurred vision	PNS	PNS, eyes	PNS	*Aspergillus* species[a]	PNS
2	72/F	DM, old CVA	no	Headache, multiple cranial nerve palsies	PNS	PNS, eyes, Lungs[b]	PNS	*Aspergillus* species[a]	PNS
3	65/M	DM	no	Headache, blurred vision, ptosis, multiple cranial nerve palsies	PNS	PNS, eyes	PNS, brain	*Aspergillus* species[a]	PNS
4	78/M	DM, HT	no	Headache	PNS	PNS	PNS, brain	*Aspergillus fumigatus*	PNS, brain
5	36/F	ALL	yes	Headache, fever, alteration of consciousness, brain herniation	Lungs	Lungs	BAL, brain	*Aspergillus fumigatus*	Lung, brain
6	55/M	DM	no	Headache, seizures, alteration of consciousness, multiple cranial nerve palsies	PNS	PNS	no	*Aspergillus* species[a]	Nasopharynx
7	68/F	no	no	Fever, alteration of consciousness, multiple cranial nerve palsies	PNS	PNS	PNS, brain	*Aspergillus fumigatus*	PNS

PNS = paranasal sinus; DM = diabetes mellitus; ALL = acute lymphoid leukemia; CVA = cerebrovascular accident; HT = hypertension; BAL = bronchoalveolar lavage
[a]histological evidence of branched septate hyphae, suggestive pf aspergillosis; [b]postmortem autopsy finding

on both CT and MRI was the paranasal sinuses (6/7; 85.7%) followed by the cavernous sinuses (4/7; 57.1%), nasopharynx (2/7; 28.6%) and optic nerve (2/7; 28.6%). The paranasal sinuses involved in 6 patients in decreasing frequencies were ethmoid sinus (5/6; 83.3%), maxillary sinus (4/6; 66.7%), sphenoid sinus (4/6; 66.7%) and frontal sinus (2/6; 33.3%). Optic nerve involvement in two patients were an infiltrative lesion in one (case 1) and bilateral optic neuritis in the other (case 3).

All patients received intravenous amphotericin B with the median accumulative dose of 1,700 mg (range 500-3,120 mg) and the median duration of treatment of 53 days (range 20-75 days). One patient (case 2) received a total dose of 500 mg of intravenous amphotericin B followed by 8,850 mg of intravenous liposomal amphotericin B. However, there was no clinical improvement.

All patients underwent extensive surgery, except for one patient (case 6) who refused surgery. The mortality rate was 85.7% (6/7). In all the patients who died, the median time from diagnosis and treatment to death was 56.5 days (3-720 days). One patient (case 7) was cured after treatment with extensive surgery and intravenous amphotericin B with a total dose of 3,006 mg, followed by oral itraconazole 600 mg/day for 6 months. However, she had a mild memory deficit on follow-up after the treatment.

Case report

From these 7 patients with CNS aspergillosis, we describe one patient who had an interesting clinical presentation and course. This patient (case 7) had no underlying disease and survived after extensive surgery to-

Table 2
Clinical findings in 7 patients with CNS aspergillosis.

Clinical findings	Numbers
Median age at diagnosis, years (range)	65 (36-78)
Symptoms and signs (%)	
Headache	6/7 (85.7%)
Multiple cranial nerve palsies	5/7 (71.4%)
Optic nerve (CN. II)	3/5
Oculomotor nerve (CN. III)	3/5
Trochlear nerve (CN. IV)	3/5
Trigeminal nerve (CN. V)	2/5
Abducens nerve (CN. VI)	3/5
Facial nerve (CN. VII)	1/5
Vestibulocochlear nerve (CN. VIII)	1/5
Glossopharyngeal nerve (CN. IX)	2/5
Vagus nerve (CN. X)	2/5
Alteration of consciousness	3/7 (42.9%)
Visual loss	2/7 (28.6%)
Fever	2/7 (28.6%)
Seizures	1/7 (14.3%)
Median duration of the symptoms and signs, days (range)	60 (8-180)
Median time to get diagnosis and treatment after admission, days (range)	8 (5-30)

gether with a high cumulative dose of intravenous amphotericin B.

Case 7, A 68-year-old woman who had no previous underlying disease was admitted because of a progressive deterioration of consciousness with low-grade fever for 6 months. Six months before admission, she had low-grade fever, fatigue, intermittent rhinorhea and urinary incontinence but she was able to work and attend to herself. Three months prior to admission, she was checked at a private hospital. Abdominal ultrasonography was done and showed a gallstone. Other laboratory findings were unremarkable. Laparoscopic cholecystectomy was performed and the pathological diagnosis was chronic cholecystitis. After surgery, she still felt fatigued and became drowsy. These symptoms slowly progressed and one month before admission ptosis of the left eye was noted. During this period she was seen and investigated at urology and ophthalmology clinics for urinary incontinence and ptosis, respectively. The neurologist was consulted since she was drowsy. Physical examination revealed bilateral ptosis being more severe on the left, generalized muscular weakness of grade 4/5. Frontal lobe signs including a palmomental reflex and grasp reflex were demonstrated. An MRI of the brain (Fig 1 A, B) revealed multiple ring enhanced lesions of both frontal lobes with moderate surrounding edema. Moderate to severe pansinusitis was also noted. Craniotomy revealed abscesses with yellowish pus and a naso-ethmoidal encephalocele defect. Pathology of the excised abscesses showed septate hyphae and dichotomous branching of fungus compatible with aspergillosis. Culture of the pus yielded *Aspergillus fumigatus*. Prior to craniotomy, rhinoscopy and tissue biopsy of left middle meatus was done. The tissue biopsy showed acute suppurative inflammation with the presence of septate hyphae and dichotomous branching compatible with aspergillosis.

In view of the result of pathology and culture, a second extensive operation, including bilateral medial maxillectomy and sphenoidotomy, was performed about one week after the first operation. Intravenous amphotericin B 35 mg/day was administered and when the cumulative dose of intravenous amphotericin B was 3,006 mg, oral itraconazole 600 mg/day was substituted. There was improvement of the symptoms, signs and neuro-imaging findings. She was discharged from

the hospital after 3 months of admission. Oral itraconazole 600 mg/day was continued for 6 months. She could walk with a walker but still had impairment of memory.

DISCUSSION

In this retrospective study, we demonstrate that CNS aspergillosis occurred mostly in elderly persons with a median age of 65 years. Almost all patients were immunocompromised hosts. Diabetes mellitus was the most common underlying disease (57.1%). In western countries, CNS aspergillosis is proportionately more common in allogenic bone marrow transplant patients (25-50%) (Denning, 2000). The possible explanation for this difference is that there is lower incidence of bone marrow transplantation in Thailand than in western countries. Only one patient in this study had an underlying hematologic malignancy. We were unable to identify underlying disease or any predisposing factors in two patients. This finding is the same as those in previous reports which showed that CNS aspergillosis also occured in immunocompetent hosts (Kim *et al,* 1993; Chandra *et al,* 2000) but the incidence was much lower than in immunocompromised hosts. In this study, only one patient received immunosuppressive therapy before developing clinical CNS aspergillosis.

Among the *Aspergillus* species, *Aspergillus fumigatus* was the most frequent strain, which causes human aspergillosis (Denning, 2000; Kim *et al,* 1993), compatible with our findings. It was found in three patients in whom *Aspergillus* species could be identified from a culture. In this study, the direct extension from paranasal sinuses, which was the most common route of infection, differed from previous reports in which CNS aspergillosis arose most commonly from hematogenous spread from the lungs (Beal *et al,* 1982; Bodey and Vartivation, 1989).

The important clinical presentations observed in this study were chronic headache, multiple cranial nerve palsies and alteration of consciousness. The long duration of symptoms and signs prior to admission supported the hypothesis that this opportunistic infection was a slowly progressive disease. It was clinically asymptomatic until severe damage of the central nervous system occurred. Once the infection became symptomatic it progressed rapidly and resulted in a fatal outcome. Only 2 patients in this study had fever, therefore normothermia does not rule out CNS aspergillosis.

Laboratory findings, including complete blood counts and serum sodium levels were nonspecific and indistinguishable from other infec-

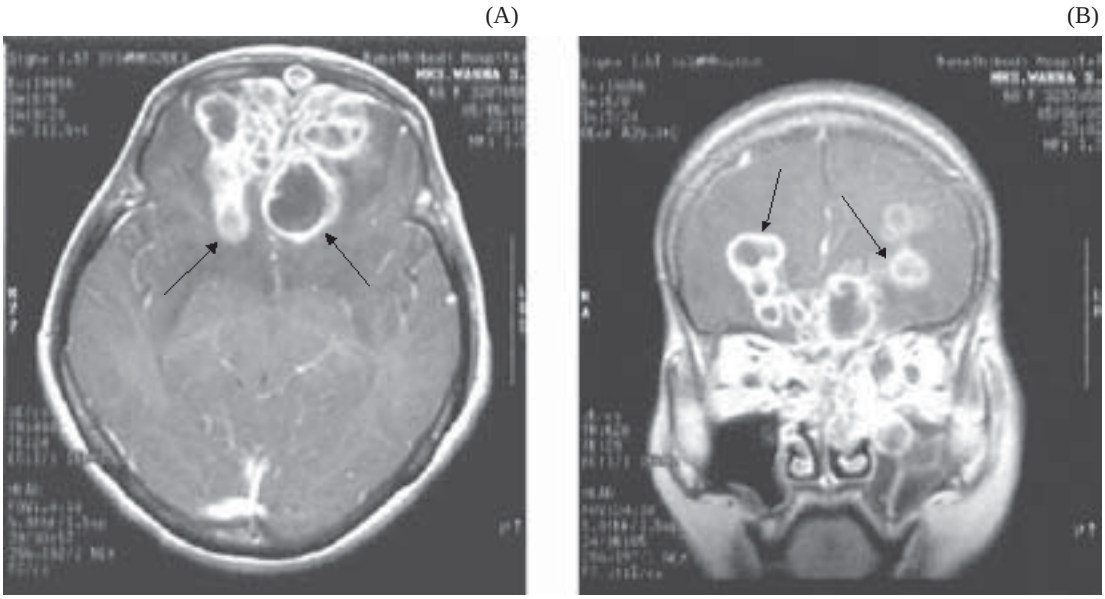

Fig 1–A-axial view. B-coronal view of an MRI of the brain of case 7 showed multiple ring enhanced lesions of both frontal lobes (*arrows*) with moderate surrounding edema.

tive processes. The definitive diagnosis depended on tissue biopsy only.

Neuro-imaging findings of CNS aspergillosis were variable and depended upon the pathological process and the host status. They were usually nonspecific and indistinguishable from other inflammatory processes. Enzyman *et al* (1980) reviewed the CT appearance of the parenchymal fungal infection of the central nervous system in the immunocompromised patients and concluded that the appearance of the CT seems to depend less on the specific infecting organism and more on the host's reaction to it. The less frequent, but characteristic, CT findings of CNS aspergillosis were hemorrhagic features due to propensity for invasion and rapid increase in the size and number of lesions over 3-8 days. Asdown *et al* (1994) reported three different neuro-imaging patterns of CNS aspergillosis in immunocompromised patients as follows:

1) Multiple areas of embolic infarction that showed hypodensity on CT scans or hyperintensity on a T_2-weighted MRI involving the cortex and/or subcortical white matter.

2) Multiple intracerebral abscesses that showed irregular and low signal intensity on a T_2-weighted MRI.

3) Dural enhancement associated with enhanced lesions in the adjacent paranasal sinuses or calcaria or optic nerve sheath.

In our study, the most common pattern was multiple lesions with ring enhancement. The MRI in 4 patients showed lesions of hypointense signal on T_2- weighted images and/or dural enhancement.

The treatment of CNS aspergillosis is composed of extensive surgery and medical treatment. Extensive surgery is the mainstay of treatment since intravenous amphotericin B penetrates poorly into the CNS (Lawrence *et al,* 1980). Moreover, the side effect of the drug is the major limitation for higher doses and long durations of treatment. Although there are many reports of successful treatment of CNS aspergillosis with surgery and medical treatment (Conen *et al,* 1962; Burton *et al,* 1972; Elgamal *et al,* 2000; Ng *et al,* 2000) including the use of intravenous liposomal amphotericin B (Rodriguez *et al,* 1999; Sungkanuparph *et al,* 2001) and the use of high dose oral itraconazole for long term therapy (Sanchez *et al,* 1995; Imai *et al,* 1999), the prognosis of this disease is still very poor with mortality rates ranging from 75-100% (Young *et al,* 1970; Denning *et al,* 1990). In this study, only one patient survived after aggressive surgery and a long duration of antifungal treatment. In the six patients who died, the median time from diagnosis and treatment to death was 56.5 days (range 3-720 days) which was rather short in spite of aggressive treatment. Possible reasons for this unfavorable prognosis are the delay in diagnosis and treatment and its high virulence. In our study, the median duration of symptoms prior to admission was 60 days (8-180 days) and the median time taken to get the clinical diagnosis and treatment after admission was 8 days (5-30 days). As mentioned above, this disease usually progresses rapidly once the symptoms have occurred. Therefore, treatment at that point may be too late for some patients even with appropriate treatment. Early diagnosis and treatment may improve the prognosis. The awareness of the prevalence of fungal sinusitis in immunocompromised patients may help in making an early diagnosis and extensive surgical debridement should be performed at the earliest stage of the invasive fungal sinusitis for a more successful outcome (Sungkanuparph *et al,* 2001). Other factors that may influence a favorable outcome were summarized by Klein *et al* (1983) as follow:1) a solitary lesion without disseminated aspergillosis; 2) well-demarcated small conglomerated abscesses; 3) easily accessible location; and 4) paucity of preoperative symptoms and signs.

In conclusion, CNS aspergillosis should be kept in mind in the elderly with diabetes who present with chronic headache, multiple cranial nerve palsies and alteration of consciousness accompanied by sinusitis. This disease remains a catastrophic opportunistic infection in spite of current intensive and aggressive treatment. Further studies to identify the most effective drug therapy, including the dose and duration of treatment, are needed, although this may be difficult due to the very low incidence of this disease.

REFERENCES

Ashdown BC, Tien RD, Felsberg GJ. Aspergillosis of the brain and paranasal sinuses in immunocompromised patients: CT and MR imaging findings. *Am J Roentgenol* 1994; 162: 155-9.

Beal MF, O'Carroll CP, Kleinman GM, Grossman RI.

Aspergillosis of the nervous system. *Neurology* 1982; 32: 473-9.

Bodey GP, Vartivation S. Aspergillosis. *Eur J Microbiol Infect Dis* 1989; 8: 413-37.

Burton JR, Zachery JB, Bessin R. Aspergillosis in four renal transplant recipients. Diagnosis and effective treatment with amphotericin B. *Ann Intern Med* 1972; 77: 383-8.

Chandra S, Goyal M, Mishra NK, Gaikwad SB. Invasive aspergillosis presenting as a cavernous sinus mass in immunocompetent individuals; report of 3 cases.*Neuroradiology* 2000; 42: 108-11.

Conen PE, Walker GR, Turner JA, *et al.* Invasive primary aspergillosis of the lung with cerebral metastasis and complete recovery. *Dis Chest* 1962; 42: 88-94.

Darras-Joly C, Veber B, Bedos JP, Gachot B, Regnier B, Wolff M. Nosocomial cerebral aspergillosis: A report of 3 cases. *Scand J Infect Dis* 1996; 28: 317-9.

Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: a review of 2121 published cases. *Rev Infect Dis* 1990; 12: 1147-201.

Denning DW. *Aspergillus* species. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases, 5th ed. Philadelphia: Churchill Livingstone, 2000: 2674-85.

Elgamal EA, Murshid WR. Intracavitary administration of amphotericin B in the treatment of cerebral aspergillosis in a nonimmune-compromised patient: case report and review of the literature. *Br J Neurosurg* 2000; 14: 137-41.

Enzymann DR, Brant-Zawadzki M, Britt RH. CT of central nervous system infections in immunocompromised patients. *Am J Roentgenol* 1980; 135: 263-7.

Haran RP, Chandy MJ. Intracranial *Aspergillus* granuloma. *Br J Neurosurg* 1993; 7: 383- 8.

Imai T, Yamamoto T, Tanaka S, *et al*. Successful treatment of cerebral aspergillosis with a high oral dose of itraconazole after excisional surgery. *Intern Med* 1999; 38: 829-32.

Kim DG, Hong SC, Kim HJ, *et al*. Cerebral aspergillosis in immunologically competent patients. *Surg Neurol* 1993; 40: 326-31.

Klein HJ, Richter HP, Schachenmayr W. Intracerebral *Aspergillus* abscess: case report. *Neurosurgery* 1983; 13: 306-9.

Lawrence RM, Hoeprich PD, Jagdis FA, Monji N, Huston AC, Schaffner CP. Distribution of doubly radiolabeled amphotericin B methyl ester and amphotericin B in the nonhuman primate *Macaca mulatta. J Antimicrobiol Chem* 1980; 6: 241-9.

Ng A, Gadong N, Kelsey A, Denning DW, Leggate J, Eden OBl. Successful treatment of aspergillus brain abscess in a child with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2000; 17: 497-504.

Oppe W. Zur Kenntnis der Schimmel Mykosen beim Menschen. *Zentralbl Allg Pathol* 1897; 8:301-6.

Pagano L, Ricci P, Montillo M, *et al*. Localization of aspergillosis to the central nervous system among patients with acute leukemia: report of 14 cases. *Clin Infect Dis* 1996; 23: 628-30.

Rodriguez DL, Lopez CA, Cobos EB, Blanco AJ, Fernandez AS, Araujo LF. Invasive cerebral aspergillosis in a patient with aplastic anemia. Response to liposomal amphotericin and surgery. *Haematologica* 1999; 84: 758-9.

Sanchez C, Mauri E, Dalmau D, Quintana S, Aparicio A, Garau J. Treatment of cerebral aspergillosis with itraconazole: do high doses improve the prognosis? *Clin Infect Dis* 1995; 21: 1485-7.

Sharma BS, Khosla VK, Kak VK, *et al.* Intracranial fungal granuloma. *Surg Neurol* 1997; 47: 489-97.

Sungkanuparph S, Sathapatayavongs B, Kunachak S, Luxameechanporn T, Cheewaruangroj W. Treatment of invasive fungal sinusitis with liposomal amphotericin B: a report of four cases. *J Med Assoc Thai* 2001; 84: 593-601.

Torre-Cisneros J, Lopez OL, Kusne S, *et al*. CNS aspergillosis in organ transplantation: a clinicopathological study. *J Neurol Neurosurg Psychiatry* 1993; 56: 188-93.

Viriyavejakul P, Phudhichareonrat S, Boonpasat Y, *et al.* Intracerebral hemorrhage due to nosocomial aspergillosis following neurosurgery. *Southeast Asian J Trop Med Public Health* 1999; 30: 154-6.

Visudhiphan P, Bunyaratavej S, Khantanaphar S. Cerebral aspergillosis: report of three cases. *J Neurosurg* 1973; 38: 472-6.

Walsh TJ, Hier DB, Caplan LR. Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. *Ann Neurol* 1985; 18: 574-82.

Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; 175:1459-66.

Young RC, Bennett JE, Vogel CL, Carbone PP, DeVita VT. Aspergillosis: the spectrum of the disease in 98 patients. *Medicine (Baltimore)* 1970; 49: 147-73.