# Cerebral Aspergillosis in Immunologically Competent Patients

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**Aspergillosis of the central nervous system is a rare disease, especially if the patient's immune system is not compromised. The authors report three cases of cerebral aspergillosis in the immunocompetent state: a rhinocerebral form in a diabetic patient, a direct extension from chronic *Aspergillus* otitis media, and a postoperative *Aspergillus* brain abscess after brain tumor surgery. In spite of the poor prognosis of cerebral aspergillosis, two of the patients survived. The pathogenesis, predisposing factors, radiologic findings including magnetic resonance image, and the outcome are presented. The pertinent literature of cerebral aspergillosis is also reviewed.**

KEY WORDS: Aspergillosis; Brain abscess; Fungus; Immunocompetent; Magnetic resonance image

Although cerebral aspergillosis had been a rare disease and very few cases had been reported until the 1970s, this is no longer the situation due to the widespread use of corticosteroids, cytotoxic drugs, and antibiotics (3,5,10,11,14,15,17,18,20–23). Immunocompromised patients with underlying malignant diseases, organ transplantations, and even acquired immune deficiency syndrome (AIDS) would all be candidates for the nonpathogenic fungal infection.

However, cerebral aspergillosis in patients with apparently intact immune systems is still rare. The authors present three cases of cerebral aspergillosis without apparent immunocompromising diseases during the 5-year period (1986–1991). All patients underwent surgery and were diagnosed pathologically. The pathogenesis, predisposing factors, radiologic findings, and the result of treatment are discussed.

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## Case 1

A 41-year-old man was admitted with the chief complaint of progressive left orbital pain for 3 weeks. He had suffered from poorly controlled diabetes mellitus for about 10 years. He was known to have chronic paranasal sinusitis due to unknown fungus and had had intermittent treatment at another clinic for several years. Though he became blind at about the same time, the blindness was neglected until the left orbital pain became severe. On admission total bilateral blindness with optic atrophy was observed. Computed tomography (CT) on admission showed haziness of the left sphenoid sinus, which extended to the anterior cranial fossa and lined the posterior part of it (Figure 1).

At the time of the left frontal craniotomy, yellow-grayish granulation tissue was found in the extradural space between the planum sphenoidale and the dura of the anterior frontal base. The lesion was destroying the bony structure and extended through the left optic foramen into the retroorbital space; it was removed totally. The left orbital pain disappeared after operation. Though the strain of the fungus could not be identified from the culture, the pathological examination showed numerous branching hyphal organisms intermingled with fibroblastic proliferation and small round cell infiltration, occasionally forming microabscesses. The mycelia were slender and branching in acute angles consistent with aspergillosis (Figure 2). Intravenous amphotericin B, 50 mg per day was administered for 6 weeks and was well tolerated. At a follow-up 30 months later, the patient was free of symptoms except for two episodes of seizure which were controlled with valproic acid.

## Case 2

A 62-year-old man was admitted to the Department of Otorhinolaryngology due to the sudden development of left facial palsy after having suffered from chronic otitis media for decades. Radical mastoidectomy and labyringectomy with facial nerve decompression were performed. Cerebrospinal fluid leakage was found immediately after the operation and repaired the next day. The



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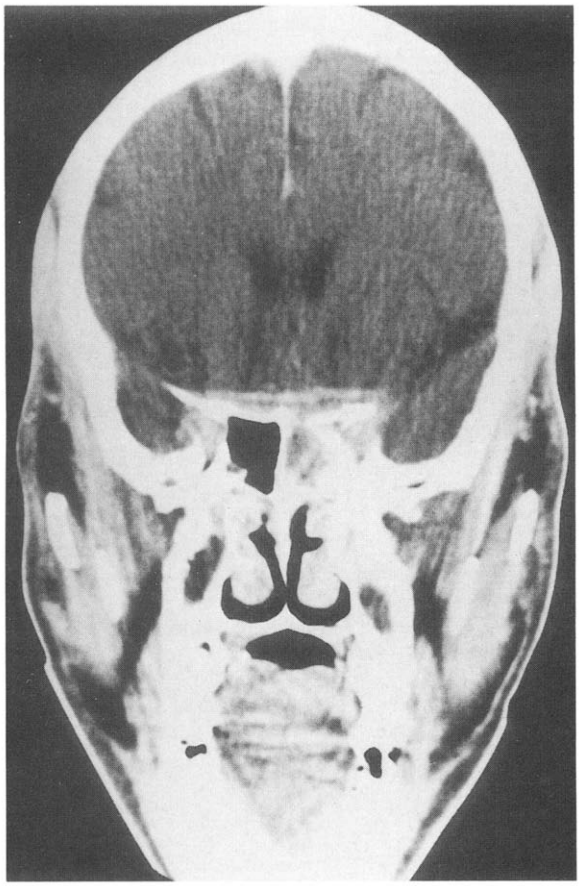

**Figure 1.** *Contrast-enhanced coronal CT scan of case 1. The abscess involves the left sphenoid sinus and extends intracranially to the posterior part of the anterior cranial fossa, lining the frontal base.*

lesion was diagnosed as aspergillosis by pathological examination. Systemic amphotericin B was administered for only 4 days due to severe side effects (fever, chills, and anorexia). Though the left facial palsy showed slight improvement, the patient began to experience a dull headache from the ninth month after surgery. The headache became intractable and the gentleman was admitted to the neurosurgical department; he was drowsy, and left cerebellar dysfunctions were observed. A CT on readmission showed moderate hydrocephalus and a lesion with strong enhancing walls in the left cerebellopontine angle (Figure 3). A left suboccipital craniectomy was done. The dura was firmly adherent to the underlying cerebellar cortex; white creamy pus was aspirated. Though total excision of the abscess wall was attempted, the anteromedial part showed firm attachment to the brain stem so it could not be removed. The removed specimen revealed an organized abscess wall. The abscess cavity contained necrotic debris and scattered clumps of fungi, reminiscent of a fungal ball. The organism consisted of clusters of slender angular branching hyphae with prominent septation. The wall consisted of dense collagenous tissue. Adjacent cerebellar tissue showed reactive gliosis and chronic inflammatory cell infiltration. Foci of necrosis and neutrophilic infiltration were seen. Epithelioid cells with palisading features and multinucleated giant cells were also seen around the granulomas.

Postoperatively, the patient was drowsy and aspiration pneumonia developed. He showed respiratory failure from week 6 on and fell into a coma. In spite of intensive medical care for pneumonia and respiratory failure, the pneumonia was intractable and he expired 6 months postoperatively. No organism was identified from the culture.

## Case 3

A 37-year-old woman was admitted due to dull headache which developed 2 months prior to admission. She had been operated on with the diagnosis of convexity meningioma on the left cerebellum at another hospital 9 months before this admission. The pathological diagnosis was meningotheliomatous meningioma, and the postoperative course was uneventful.

On examination, she was alert and well oriented. Bilateral papilledema was observed. There were no evident cerebellar dysfunction. CT and magnetic resonance imaging (MRI) showed an irregular-shaped lesion in the left cerebellar hemisphere, the same location of the previous tumor. The wall was well enhanced on both CT and MRI (Figure 4). The configuration of the wall was irregular in shape and thickness; a small daughter lesion was observed. The operation was performed through the previous route. The dura was thick and a yellow-grayish discolor. Yellow, chalky, purulent content leaked out on opening the dura. The thick, sticky wall of the abscess was excised completely without difficulty. The pathologic examination showed a well-organized abscess wall and necrotic debris in the center. Numerous branching mycelial structures were scattered through the necrotizing lesion which involved cerebellar tissue. The organisms were slender and septate, and acutely branching, which are indicative of the *Aspergillus* species. Postoperatively, she was treated with 20 mg of amphotericin B plus 7 mg of 5-fluorocytosine per day for 4 weeks. She is in good health after 8 months of postoperative follow-up.

## Discussion

### *Pathogenesis*

Among the *Aspergillus* species, it is known that *Aspergillus fumigatus* is the most frequent strain producing the human aspergillosis.

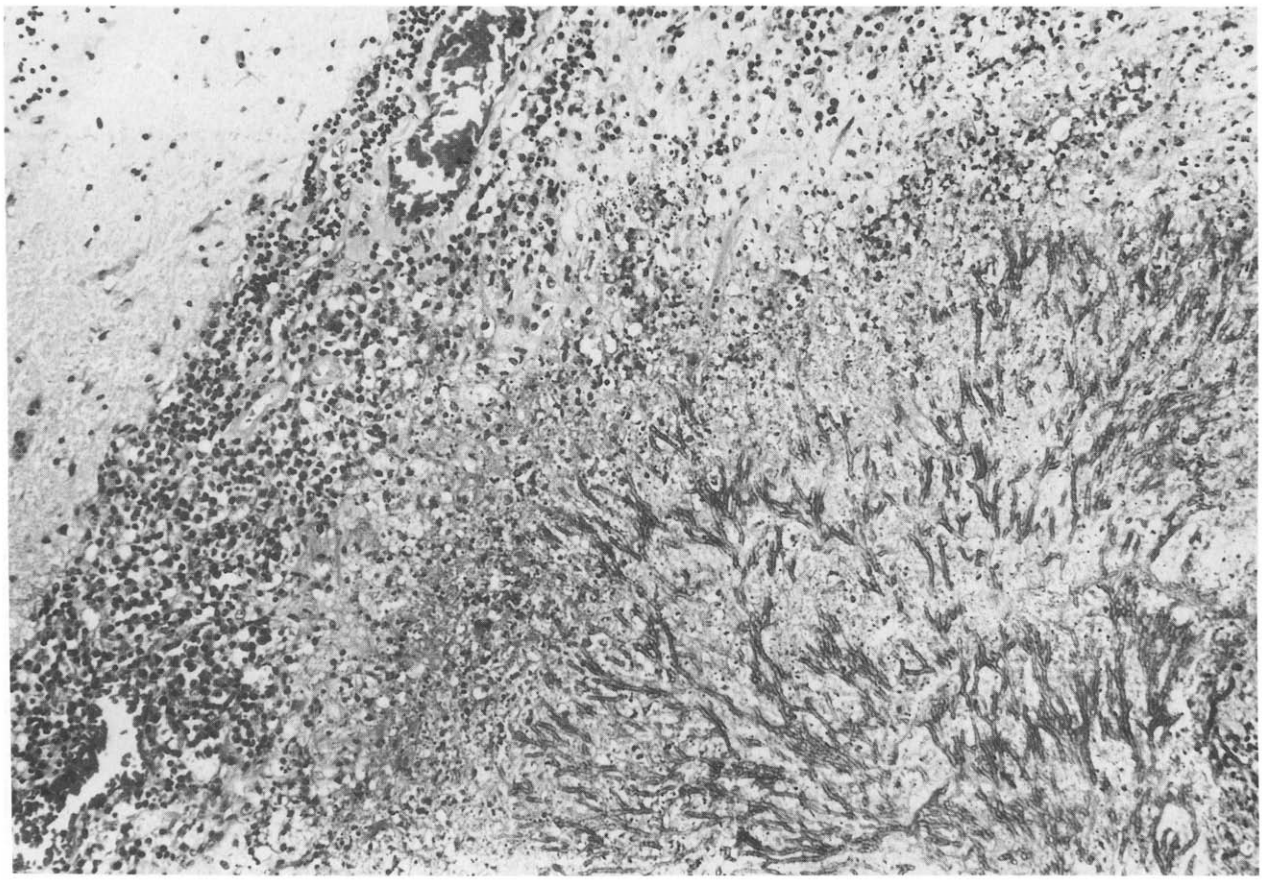

**Figure 2.** *Microscopic view of cerebral aspergillosis. A large, necrotic focus harboring numerous, thin, branching hyphae is surrounded by a zone of lymphohistiocytic cells. H & E × 100 (case 1).*

Cerebral aspergillosis arises most commonly from the hematogenous spread from the lung, and occasionally from the direct extension of paranasal sinus, middle ear or orbital infection (1,3,4,11,15,16,19–21). Direct introduction of *Aspergillus* may be also associated with intracranial surgery. We could find only six cases in the literature of cerebral aspergillosis occurring as a complication of neurosurgical procedures (Table 1) (2,7,8, 19,21). If the cases of Feely and Steinberg [7] were excluded in which the cerebral aspergillosis were thought to be superimposed upon the long-standing recurrent meningitis after yttrium-90 ($^{90}$Y) implantation into the sella, then the interval between the primary surgery and the onset of symptoms of cerebral aspergillosis would range from the immediate postoperative period to 1 year. Our case 3 developed a dull headache at 8 months after the first operation for posterior fossa meningioma. The postoperative infection (brain abscess) was the first choice of differential diagnosis; aspergillosis was hardly taken into consideration because there was no evidence of any predisposing factor for it and aspergillosis is inherently very rare.

### *Perdisposing Factors*

Aside from the immunocompromised status, such as leukemia, lymphoma, or other malignant disease, and organ transplantation, the conditions that might have made the patients more susceptible to the cerebral aspergillosis could be summarized as follows according to a review of the literature: five cases of chronic alcoholism (3,12,17,19,22), four cases of drug addiction (11,16,19, 22), four cases of sinusitis (2,15), three cases of occupational origin (millers and farmers) (4,13,20), three cases of hepatic failure (22), two cases of Cushing's syndrome (22), two cases of head trauma (2,3), and one case each of diabetes mellitus, mitral heart disease, and quadriplegia (3,17). There were only four cases of cerebral aspergillosis in the apparently "normal" status without any predisposing factors (11,15,21). The importance of systemic administration of corticosteroid as a predisposing factor for aspergillosis is well known and should be appreciated in current neurosurgical practice. Our case 1 had diabe-

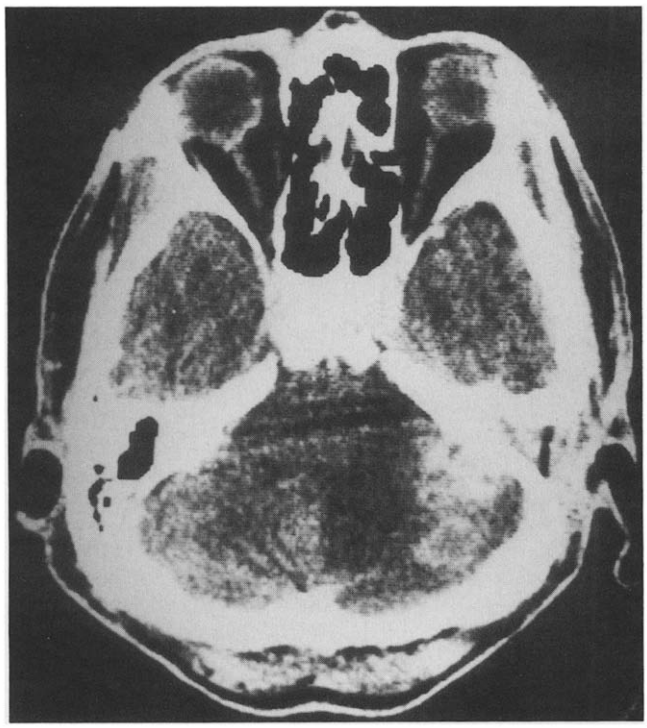

**Figure 3.** *Contrast-enhanced CT scan of case 2. Two abscesses are conglomerated at the left cerebellopontine angle. The adjacent left petrous bone lost its air content.*

tes mellitus and chronic paranasal sinusitis, and case 2 had been suffering from chronic otitis media. Both of those cases had sufficient conditions to develop aspergilloma in the adjacent intracranial space. However, there were no predisposing factors in case 3 except the tumor surgery itself. Because completeness of aseptic laminar flow could not be guaranteed in the operating room, the chance of contamination by *Aspergillus* in the air of the operating theater could not be ruled out.

### *Radiologic Findings*

The CT findings of cerebral aspergillosis are variable and depend upon the pathological process and the host factors (6,20,22), they are usually nonspecific and indistinguishable from other inflammatory processes (2,3,12,22). The enhancement pattern also varies according to the immune status of the host and the pathological process. Enzymann et al. (6) reviewed the CT appearance of parenchymal fungal infection of the central nervous system in the immunocompromised patients, and concluded that the appearance of CT seems to be a function less of the specific infecting organism but more of the host's reaction to it. The less frequent but characteristic CT findings of cerebral aspergillosis are hemorrhagic features due to the propensity of the blood vessel invasion, and rapid increase in size and number of lesions over 3–8 days, those occurring in patients known to have aspergillosis in other organs. Cases 2 and 3 showed multilobulated abscess with well-enhancing walls in CT. The abscess cavity did not look dense compared to the bacterial abscesses. In our cases, there was no evidence of hemorrhage.

In our case 3, the MRI findings ruled out the possibility of tumor recurrence and favored brain abscess (low-intensity signal on $T_1$-weighted image with strong enhancement of the wall). Extensive surrounding edema is more evident on $T_2$-weighted image of MRI. The irregular-shaped wall is enhanced strongly both in CT and MRI. The abscess cavity is a low-intensity signal compared to the edematous region in every MRI scan. There were no specific features for the aspergillosis abscess except that the abscess had multiple daughter lesions and showed a shaggy appearance of the wall.

### *Diagnosis*

Diagnosis of aspergillosis only by histopathological sections would be open to some dispute because differentiating from other fungi such as *Penicillium* and *Cladosporium* is difficult (20). However, the results of culture to identify the strain of *Aspergillus* have been disappointing. It is known that the results of a culture from the central nervous system tissue may not be positive even in the disseminated disease (4,11,18). Though characteristic featuers of *Aspergillus* abscess were visible on direct smear of the pus in cases 2 and 3, the results of the cultures were negative in both cases. The diagnosis of aspergillosis could only be made on the pathological bases in the three cases. Though specific diagnosis might be possible with a serological test (16), the problems of sensitivity and availability prevent us from using it regularly.

### *Treatment and Result*

In spite of the aggressive use of amphotericin B and 5-fluorocytosine, the prognosis of cerebral aspergillosis is poor (5). Among the 36 cases of cerebral aspergillosis without immunocompromising disease, which we could collect from the world literature, only five cases survived after surgery plus chemotherapy (2,12,15,22). Klein et al (12) summarized the factors for favorable outcome in cerebral aspergillosis as follows: (1) a solitary lesion without disseminated aspergillosis; (2) well-demarcated small conglomerated abscess; (3) easily accessible location; and (4) paucity of preoperative symptoms and signs.

As per our experience with the three cases, early

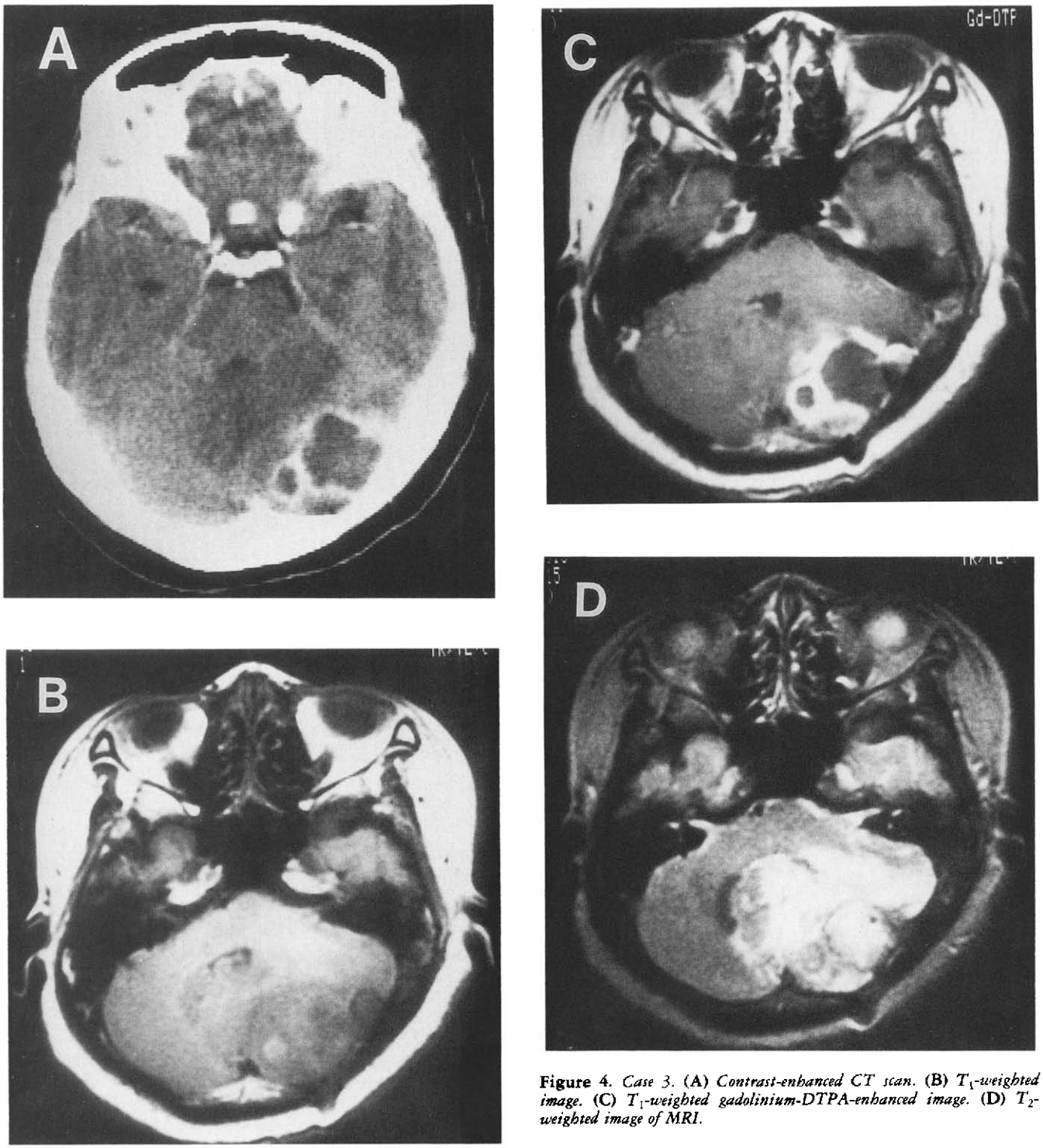


**Figure 4.** *Case 3.* **(A)** *Contrast-enhanced CT scan.* **(B)** *$T_1$-weighted image.* **(C)** *$T_1$-weighted gadolinium-DTPA-enhanced image.* **(D)** *$T_2$-weighted image of MRI.*

**Table 1.** *Summary of Six Cases of Cerebral Aspergillosis Complicating the Neurosurgical Procedures from the World Literature*

| Author (Year) | Sex/Age | Underlying Disease | Interval (surgery-sx. onset) | Pathology | Culture | Outcome |
|---|---|---|---|---|---|---|
| Visudhiphan et al (1973) | M/13 | Craniopharyngioma | A few days | Basilar artery aneurysm | (−) | Expired |
| Shapiro and Tabaddor (1975) | F/36 | Glioblastoma multiforme with hydrocephalus | A few days | Granuloma | (−) | Expired |
| Feely and Steinberg (1977) | F/57 | Acromegaly | 2 months | Meningitis | (−) | Expired |
| | M/37 | ? (DM) | 10 years | Meningitis | (−) | Recovered |
| Galassi et al (1978) | F/59 | Olfactory groove meningioma | 1 year | Multiple granuloma | *Aspergillus fumigatus* | Expired |
| Beal et al (1982) | F/22 | Medulloblastoma | 2 weeks | Meningitis | (−) | Expired |

*Abbreviations:* M, male, F, female, DM, diabetes mellitus.

diagnosis and prompt administration of amphotericin B with or without 5-fluorocytosine would have improved the overall outcome. The side effects of current chemotherapeutic agents and the narrow range of choice were the major limitations for the postoperative treatment.

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