Cerebral aspergillosis
Report of three cases

PONGSAKDI VISUDHIPHAN, M.D., SIRA BUNYARATAVEJ, M.D., F.R.C.S. (ENG), F.R.C.S. (EDIN), AND SUWARINDR KHANTANAPHAR, M.D.
Departments of Pediatrics, Surgery and Pathology, Ramathibodi Hospital, and Faculty of Medicine, Mahidol University, Bangkok, Thailand

Three patients with cerebral aspergillosis are reported. Each patient had a different lesion: a solitary brain abscess, a mycotic basilar artery aneurysm, and a massive infective intracranial hemorrhage. Aspergillosis is discussed, including its diagnosis and treatment.

KEY WORDS: aspergillus, abscess, mycotic aneurysm, arteritis, intracranial hemorrhage

ALTHOUGH there are over 350 recognized species of Aspergillus, few are pathogenic to man. Infections of the central nervous system have been ascribed to Aspergillus fumigatus, A. flavus, A. amstelodami, and A. sydowi, in that order of frequency. About 65 cases of cerebral aspergillosis have been reported; these include only six cases of solitary brain abscess, two of massive subarachnoid hemorrhage, and one of a ruptured mycotic aneurysm.

Because of the rarity of cerebral aspergillosis and the importance of neurosurgical treatment, we are reporting three cases, each of which had a different lesion.

Case 1

A 13-year-old Thai girl was admitted because of fever, headache, and abdominal pain of 4 months' duration. After 2 months of symptoms she had been diagnosed at another hospital as having purulent meningitis and had been given penicillin and chloramphenicol for 4 weeks, with some improvement. A lumbar puncture in the sixth week of treatment had yielded clear cerebrospinal fluid (CSF) which contained 25 lymphocytes/mm³, with a protein content of 85 mg% and a sugar content of 59 mg%. Two weeks before admission to our hospital she developed persistent headaches, vague abdominal pain, and nausea.

Examination. The patient was alert and well oriented. The fundi showed a moderate degree of papilledema bilaterally. There was no other neurological abnormality. Laboratory examinations were normal except for a sedimentation rate of 108 mm/hr. Gamma technetium-99 brain scan revealed a small area of increased uptake in the right parietooccipital region. Right brachial arteriography demonstrated an avascular mass in the right parietooccipital region with a slight shift of the anterior cerebral arteries to the left. Electroencephalography showed an
Cerebral aspergillosis

Operation. A clinical diagnosis of brain abscess was made, and the right parietooccipital region explored through a craniotomy. The brain was edematous, but cannulation at different depths and directions encountered no resistance, pus, or fluid. Brain tissue biopsies at different depths revealed an identical nonspecific inflammatory process with periarterial round-cell infiltration; no organism was seen in the histological section. A second craniotomy, this time in the posterior temporal region, produced the same operative and histological results.

Postoperative Course. Because of the uncontrolled increased intracranial pressure, steroid therapy was instituted and resulted in a marked improvement. The patient became dependent on the drug, however, and withdrawal only caused recurrence of symptoms. Four months after the first craniotomy she suddenly developed high fever, headache, vomiting, and lethargy. Stiffness of neck, bilateral paeilledema, and right homonymous hemianopia, which had been noted since the first craniotomy, were still present. The possibility of meningitis secondary to a ruptured brain abscess was seriously considered, but she rapidly became deeply comatose and died. A lumbar puncture done prior to her death yielded cloudy CSF with an initial pressure of 300 mm H₂O. The fluid contained 650 white blood cells/mm³; the protein content was 70 mg% and the sugar, 38 mg%. Culture of the CSF was positive for Aspergillus fumigatus.

Postmortem Examination. The brain was edematous and showed a pressure cone of the right cerebellar tonsil. The arachnoid was cloudy. A large abscess about 5 cm in diameter was found underneath the craniotomy site in the right occipital lobe; it had already ruptured into the ventricle (Fig. 1). The wall of the abscess was moderately thickened and firm. Aspergillus was identified in the histologic preparations of tissue from the area of the abscess. The culture from the pus produced Aspergillus fumigatus. Examination of the middle ears and sinuses disclosed no abnormalities.

Case 2

A 13-year-old boy was transferred to our hospital for surgical treatment of a craniopharyngioma diagnosed elsewhere. He had had progressively severe headaches and failing vision for 1 year. Physical development had been retarded since the age of 7 years. Skull films before admission had demonstrated the suprasellar calcification of a craniopharyngioma.

Examination. The patient was physically underdeveloped, with a mild degree of hypopituitarism, but was alert and oriented. He had no light perception in the left eye and could only count fingers with the right. The fundi showed severe optic atrophy bilaterally. The rest of the neurological examination was normal.

Operation and Postoperative Course. A craniopharyngioma was totally removed. The patient tolerated surgery well, but the postoperative course was stormy. Diabetes insipidus and severe electrolyte disturbances required supplements of cortisol hemisuccinate and pitressin tannate. Penicillin and streptomycin were given but a high daily fever persisted. A lumbar puncture performed on the 8th postoperative day yielded slightly cloudy CSF with 130 white blood cells/mm³, mostly polymorphonuclear. Protein content was 100 mg% and sugar 40 mg%. Several cultures were negative for bacteria and fungus. The cells in successive CSF examinations varied from 130 to 2500/mm³ and were mostly polymorphonuclear. Various kinds of antibiotics including Amphotericin B were given for 5 weeks, to
no avail. The patient's condition deteriorated rapidly, and he died about 6 weeks after surgery.

Postmortem Examination. A large amount of blood was found in the basal subarachnoid space. When this was cleared away no tumor remnant could be found. The hypothalamic region was grossly intact. There was a large aneurysm of the upper end of the basilar artery, which had ruptured and probably caused death (Fig. 2 left). Microscopic examination of the aneurysm showed that it was mycotic in nature; the numerous hyphae were identified as Aspergillus (Fig. 2 right); the fungi were not found elsewhere in the body.

Case 3

A 5-year-old Thai girl was referred to our hospital because of fever, vomiting, jaundice, and coma of 3 days' duration. Examination at the provincial hospital on the first day of illness noted that the liver was palpable 1 cm below the right costal margin and that the neurological examination was normal. On the following day she began to vomit coffee ground material, and the stool was loose and tarry. Intravenous Ampicillin and glucocorticoid were given. The patient's condition deteriorated rapidly and she became comatose on the third day of the illness.

Examination. The child was febrile, deeply comatose, and moderately anemic, and jaundiced. The liver was palpable 4 cm below the right costal margin; its surface was smooth and slightly tender. The spleen was just palpable. The pupils were equal and reacted normally to light. Both fundi were normal. There were no localizing neurological signs. Blood examination showed marked leucocytosis of 23,000/mm³ with 67% polymorphonuclear cells. Total serum bilirubin was 3.2 mg%, and 1.05 mg% direct. The diagnosis of gram-negative bacterial sepsis was made, and the patient gradually improved with antibiotic and vitamin K therapy, becoming more respon-
Cerebral aspergillosis

tive on the third day. The temperature, however, remained constantly high. On the tenth day of hospitalization she suddenly became deeply comatose again. The neck was stiff. A lumbar puncture yielded bloody CSF and an opening pressure of 420 mm. She died before carotid arteriography could be done.

Postmortem Examination. The brain showed generalized edema. The right cerebral hemisphere was larger than the left. There was a moderate degree of subarachnoid hemorrhage on the convexity and at the base of the right cerebral hemisphere. There was midline herniation of the right cingulate gyrus. The basal cistern was filled with blood. The blood vessels of the circle of Willis were normal. On sectioning the brain the ventricular system was found filled with blood clots. There was an area of intracerebral hemorrhage within the right temporal lobe which had ruptured into the ventricular system (Fig. 3). Further sections showed multiple abscess formations involving the white matter of the left parietal lobe and the right temporal lobe. In areas of abscess formations, Aspergillus organisms were identified microscopically. Section of the blood clot from the area of the intracerebral hemorrhage showed inflammation of the vascular wall which was presumably a part of a mycotic aneurysm that had ruptured. Aspergillus organisms were also found in kidneys, liver, and endocardium. Culture of the pus from these abscesses produced Aspergillus flavus.

Discussion

Aspergillus infection usually appears in debilitated patients or in patients whose immune mechanisms have been modified by severe alcoholism, advanced pulmonary tuberculosis, hepatitis, addiction to heroin, or similar conditions. There appears to have been a recent increase in the number of cases of human cerebral aspergillosis. Between 1897 and 1950 only 12 cases had been reported. The majority of cases have occurred since then. Some authors believe that this reflects the increased use of corticosteroids, cytotoxic agents, and antibiotics; all three of our patients had received these drugs.

In many cases the exact pathway by which Aspergillus reaches the brain cannot be established, but in the large majority it seems to be by hematogenous dissemination from a primary focus in the lung, or by direct extension from the ear, nose, and paranasal sinuses. Most cases of cerebral aspergillosis are associated with systemic infection.

Only a few documented cases of solitary intracranial brain abscess have been recorded. Our first case had only a solitary brain abscess of the occipital lobe without a demonstrable primary focus elsewhere in the body. We believe that the onset of the disease in this patient was meningitis which did not respond to conventional treatment; the disease progressed slowly to infect the brain tissue. The use of antibiotics and glucocorticoid therapy could possibly have accelerated the disease process. At the time of the craniotomy, about 2 months after the onset of the disease, the brain was swollen but we could find no abscess nor localized granulomatous lesion. The biopsy studies showed a nonspecific inflammatory reaction but no bacterial organism or hyphae of the fungus. It seemed to us that, at the time of the craniotomy, the patient probably had only focal cerebritis, and that no abscess had yet formed. The infection was then walled off, and, with the help of prolonged use of steroids and antibiotics, became a

Fig. 3. Case 3. Brain section showing a large intracerebral hemorrhage within the right temporoparietal region, and another small abscess in the opposite side.
large abscess underneath the craniotomy site. The solitary brain abscess caused by *Aspergillus fumigatus* extended into both cerebral hemispheres and the cerebellum. The locations of the six solitary cerebral abscesses reported as caused by this organism were frontal lobe, temporal lobe, and cerebellum. Our case is the only abscess reported in the occipital region.

*Aspergillus* commonly invades the walls of both large and small blood vessels, producing thrombosis and hemorrhagic necrosis. However, there have been only two cases reported in which *Aspergillus* had been associated with massive subarachnoid hemorrhage.\(^3\) One patient had mycotic meningitis and mycotic infection of the brain with arteritis plus a subarachnoid hemorrhage due to rupture of the internal carotid artery without any aneurysm.\(^11\) Another patient was recently described as having a large ruptured mycotic aneurysm of the basilar artery. A large number of *Aspergillus* organisms were seen in the wall of this aneurysm.\(^11\)

Our second case had a subarachnoid hemorrhage caused by rupture of a mycotic aneurysm on the basilar artery. A large number of *Aspergillus* organisms were seen in the wall of this aneurysm. The size and location of the mycotic aneurysm in our second case were similar. The third case was a farm boy who probably had *Aspergillus* infection of the lungs which disseminated to the brain and other organs. The important point of this case was that he suddenly developed a massive intracerebral hemorrhage which required immediate neurosurgical intervention. It was unfortunate that the patient deteriorated rapidly and died before any surgery could be performed. We have been unable to find any other report of a massive intracerebral and subarachnoid hemorrhage due to *Aspergillus flavus* infection. The cause of bleeding in our patient was probably related to the cerebral arteritis and ultimate aneurysmal rupture.

### References


*Address reprint requests to: Pongsakdi Visudhiphan, M.D., Faculty of Medicine, Mahidol University, Ramathibodi Hospital, Rama VI Road, Bangkok 4, Thailand.*