Cerebral Aspergillosis

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The four cases of intracranial aspergillosis presented encompass most of the recognized clinical and pathological spectrum of this disease. The clinical settings which should arouse suspicion of aspergillus infection are discussed. The diagnostic modalities and therapeutic maneuvers available are also considered.

In spite of an expanding list of settings favoring fungal infections, less than 70 cases of central nervous system aspergillosis have been reported. This relative paucity of cases attests to the rarity of this infection in any medical center. Experience in this large urban center had been nil until the four patients described below were treated in this hospital. The features exhibited in these cases encompass many of the pathologic and clinical findings seen in central nervous system aspergillosis. We will emphasize in this report clinical aspects of both diagnosis and treatment.

Case Reports

Case 1: This 31-year-old black male was brought to the emergency room following a generalized seizure. His family reported the insidious onset of a non-productive cough three months earlier. Two months prior to admission he experienced the first of several generalized seizures; no investigation was undertaken at that time. A ten-pound weight loss occurred in a setting of moderate ethanolic abuse and a cigarette habit of one pack per day. There was no history of tuberculosis, narcotic abuse, occupational exposure to fungi, nor symptoms of increased intracranial pressure. Upon admission, normal vital signs including temperature were obtained. General physical examination showed no abnormalities. Neurologic examination showed lethargy, non-fluent aphasia, right hemiparesis with the eyes tonically deviated to the right. There was no papilledema.

Lumbar puncture on admission revealed an opening pressure of 160 mm of cerebrospinal fluid. There were no cells; the protein was 83 mg%; glucose was 62 mg%. Brain scan showed discrete areas of uptake in both frontal lobes with small foci of increased uptake in other parts of the cerebral hemispheres (Fig. 1). Tuberculin skin testing was negative. The X-ray examination of the chest was normal.

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The patient progressively deteriorated within the first 24 hours after admission, prompting cerebral angiography. Since the majority of clinical findings were referable to the left cerebral hemisphere, the left internal carotid artery was studied first. This was occluded in its proximal segment (Fig. 2). Consequently the right carotid artery was studied, revealing a deep right frontal avascular mass with minimal shift of the anterior cerebral artery. The following day ventriculography was performed in the hopes of delineating a focal mass. Figure 3 demonstrates the ventriculogram which showed compression and displacement of the left frontal horn. Bilateral needle exploration of the frontal lobe yielded tissue showing small granulomas and septate hyphae consistent with aspergillosis. No discrete abscess cavity was located. The patient deteriorated and died three days after admission.

Autopsy showed multiple areas of focal necrosis consistent with cerebritis (Fig. 4A). All showed evidence of fungal infestation. Fungal arteritis explained the thrombosed left internal carotid artery. The lungs showed involvement with aspergillosis, along with aspergillosis granulomas in the walls of the major thoracic blood vessels.

**Comment:** Widespread thoracic involvement was found at autopsy, yet retrospective review of the X-ray films of the chest showed no definite roentgenographic evidence of these changes. The thoracic pathologic abnormalities were consistent with a chronic process belying the short clinical history. The rapid progression of cerebral symptoms point up the aggressive devastation caused by this organism in this patient. The lack of any factor predisposing him to infection with this organism is puzzling and unusual. Although the vascular invasion found in the chest points to hematogenous dissemination as the source of cerebral seeding, the striking feature is the restriction of extrathoracic aspergillosis to the central nervous system.

**Case 2:** This 31-year-old black female reported increasing severity of generalized headaches recently complicated by blurring of vision. Outpatient examination revealed papilledema, which prompted immediate hospitalization. Sixteen years before admission, the patient was treated for pulmonary tuberculosis; biannual examinations showed no recurrence. Parenteral narcotic addiction had ended three years earlier; she was placed on methadone maintenance. General physical examination including temperature was normal. Neurologic examination revealed only high grade papilledema; visual acuity and fields were normal.

Brain scan showed discrete areas of increased uptake in both frontal lobes with a questionable area of increased uptake in the left parietal area. Cerebral angiography did not confirm the left sided lesion, but did demonstrate a large avascular mass in the right frontal lobe.

At operation a large granulomatous mass was found within the brain parenchyma. Frozen section was consistent with aspergillum. A right frontal lobectomy left a small amount of residual aspergillum. Subsequent cultures identified the organism as aspergillus fumigatus (Fig. 4B).

Recovery from the immediate effects of the craniotomy was uneventful. The patient was started on systemic and intrathecal amphotericin B to a planned total dose of 3 gm given over six weeks. The patient was apparently tolerating this regimen without change in her neurologic status, but suddenly developed gram negative sepsis and died on the tenth postoperative day, after receiving only one-fifth of the planned dose of amphotericin B.
The general autopsy examination failed to reveal any extracranial foci of aspergillosis infection. Careful examination of the lungs, thoracic vessels and heart valves was carried out and no evidence of aspergillosis, either gross or microscopic, was found.

Examination of the nervous system showed general thickening and inflammation of intracranial and spinal meninges with accumulation of purulent exudate in the pontine cistern and in the spinal subarachnoid spaces. There was generalized cerebral edema with bilateral uncal and tonsillar herniations. Multiple granulomas were found, mostly in the gray-white matter junctions and in the periventricular areas. Generalized cerebral vasculities was demonstrated microscopically, but no evidence of aneurysm was found.

**Comment:** The widespread cerebral involvement found at autopsy was unexpected. The distribution of the microgranulomas at the gray-white junctions is frequently attributed to hematogenous dissemination from extracranial sources. However, at autopsy, we found no extracranial tissue involvement.

**Case 3:** This 36-year-old black female presented with a three-week history of bizarre behavior. Examination showed a lethargic aphasic female with a mild right hemiparesis. Brain scanning and central angiography were inconclusive. While awaiting further studies, the patient became stuporous and required external ventricular drainage. Contrast ventriculography demonstrated hydrocephalus and a left thalamic tumor encroaching upon the lateral and third ventricles. Following ventriculo-peritoneal shunting, radiotherapy was started. Shortly afterwards the patient developed peritonitis and shunt infection, treated by antibiotics and shunt removal. Two months later the focal symptoms progressed without signs of elevated intracranial pressure. Through a parietal occipital craniotomy the occipital lobe was elevated exposing the thalamic mass for biopsy. This proved to be glioblastoma multiforme. Postoperatively the shunt was replaced. Intercurrent infections were treated with a variety of antibiotics but she was afebrile for one week until her demise from progressive growth of the glioblastoma multiforme six weeks after craniotomy.

Autopsy showed two granulomas containing aspergillus organisms in the right frontal and parietal lobes, areas traversed previously by ventricular cannulae.

**Comment:** These lesions were entirely unexpected post mortem findings. It is hard to assess their clinical significance as they occurred in a patient with a neoplastic space occupying lesion. Identifying the source of these intracranial aspergillosis foci is speculative. Their location in the tracts of shunt apparatus raises the question of introduction of the organism with the shunt tubing. Another explanation would be colonization of these foreign bodies by blood borne fungi occurring in a debilitated patient.

**Case 4:** This 24-year-old white female presented with a long history of multiple cutaneous and pulmonary infections and an immune deficiency disorder characterized by an elevated IgE and 10% eosinophilia. Seven months earlier, she underwent right middle lobectomy for aspergillosis; medical treatment with amphotericin B was discon-
tinued after bone-marrow suppression occurred. Recurrent symptoms prompted complete right pneumonectomy one month later. Fever and shortness of breath led to readmission at which time the temperature was 38.3°C. Multiple skin furuncles were noted as well as dullness and absent breath sounds over the right thorax. The neurologic exam was normal. A pleural space infection with klebsiella, streptococcus, and strepfaecalis was diagnosed after thoracentesis, and the patient was treated initially with antibiotics and later by closed thoracostomy. A broncho-pleural fistula developed which was treated by thoracoplasty. Three days later the patient suddenly developed higher fever, right hemiparesis but no alteration in her level of consciousness. A lumbar puncture showed an opening pressure of 220 mm cerebrospinal fluid, protein 125 mg% and glucose of 30 mg% with no cells. A carotid angiogram showed a left temporal lobe mass. At craniotomy a small abscess containing 15 cc of pus was drained from the left temporal lobe. The pus was sterile on culture and no organisms were seen on microscopic examination. However, the pathologist identified aspergilli in the wall of the abscess. The remainder of the temporal lobe was necrotic with many thrombosed veins. Postoperatively, the patient was in septic shock. Although able to follow commands with the left side, she was never able to maintain her blood pressure off pressor agents and died on the second postoperative day.

At autopsy, disseminated aspergillus was found involving lungs and thoracic vertebrae. Sectioning the brain revealed separate areas of aspergillus cerebritis involving the anterior and posterior left frontal lobe and the left temporal lobe as well as granulomatous meningitis.Septate branching hyphae were found invading vessel walls.

Comment: This patient developed acute central nervous system aspergillosis in a setting consisting of immuno deficiency and a history of previous extracranial aspergillus infection. The hypoglycorrhoea is unusual. The acute onset of hemiparesis in an alert patient was interpreted by clinicians as a stroke; in view of the microscopic vascular invasion by aspergilli, this interpretation may have been correct.

Discussion

Infection with aspergillosis usually occurs in four settings: 1) patients whose immune response has been depressed usually iatrogenically by corticosteroids, immuno-suppressive agents or antibiotics; 2) patients whose underlying disease, whether it be toxic, such as ethanolism, or neoplastic including leukemia, has altered their ability to combat infection; 3) patients whose habits, such as narcotic addiction, predispose them to the by-pass of normal body defense mechanisms; 4) patients with occupational exposure to aspergillosis. 

Since aspergillosis is found in the soil, especially in warm damp climates and often isolated from grain products and stock feeds, occupational exposure exists where there is abundant dust formation and where grain or animal feed is handled. Aspergillosis has been found also in the dust from wig assembly and in the dust produced by workers beating dried sponges. The importance of contributing factors is underscored by a study by Carbone et al., showing an incidence of 1.7% of aspergillosis infestation in an autopsy population of patients dying with cancer.

Central nervous system involvement with aspergillosis depends in part on the clinical setting. In the series cited above, 23% of those cancer patients with aspergillosis infestation (or 0.39% of all patients in the series), had central nervous system aspergillosis, emphasizing the relative frequency of this rare infectious agent given a favorable setting. Patients with disseminated aspergillosis associated with a variety of concurrent diseases have a 60-70% chance of central nervous system involvement.9,17 The incidence of central nervous system aspergillosis in the majority of groups referred to above is, at imprecise, because of the difficulty in defining the populations at risk. The relative increase in the number of reported cases since 1970 may reflect both medical advances and changes in social habits favoring infection with aspergillus.

Aspergillus most commonly reaches the brain after forming a focus in another part of the body. Because the fungus is abundant in inhaled dust, the respiratory tract is the usual portal to entry.9 When the respiratory tract focus is in the paranasal sinuses, spread occurs to adjacent areas of brain either directly or through local venous channels.8 In this setting the frontal lobe will often be the seat of involvement. Often a pulmonary parenchymal lesion serves as the source for later hematogenous dissemination of organisms to the brain. This most probably occurred in Cases 1 and 4. Rarely aspergillosis produces an endocarditis, yet another source for hematogenous spread of organisms to the brain.30,31 Loci of involvement in the nervous system when fungal spread is hematogenous can be predicted at the gray-white matter junction as seen in Case 2. Cases have been reported documenting orbital and ear involvement with secondary local spread to adjacent areas of brain. 28,29 Direct hematogenous introduction of aspergillus has been reported in cases of blood transfusion22,30 and also as autoinoculation by narcotic addicts.36 Our experience and that of others, suggest that direct introduction of aspergillus may be associated with intracranial surgery.30

The rapidity of progression does...
I. Aspergillosis may have either pulmonary or paracranial primary infections with secondary cerebral aspergillosis producing neurological symptoms for several years before final clinical consultation. Although this multi-system involvement usually is considered "disseminated aspergillosis," the initial relatively indolent behavior appears to contradict the connotation of the term disseminated disease. In contrast patients under treatment with certain therapeutic agents or terminal cancer patients usually have truly disseminated infections which pursue a rapid course, with demise occurring within weeks.

Five basic pathologic processes can be identified in central nervous system aspergillosis; each of these pathologic pictures mirrors the clinical relationships outlined above. By far the most common form is found in debilitated patients or those with rapidly progressive dis- ease. Primary arteritis is most often seen in patients with hematogenous dissemination. However parenchymal aspergillosis with secondary invasion of cerebral blood vessels has been reported and was seen in two of our cases.22 Subarachnoid hemorrhage in cases of cerebral aspergillosis has been attributed to arterial invasion by the fungus with formation of mycotic aneurysm.6 Finally meningitis may be seen in aspergillosis.10

As stressed by others, the clinical presentation of aspergillosis of the central nervous system is polymorphic.9 There may be few neurological signs in patients whose cerebral involvement is part of an underlying debilitating disease. Patients with a rapid course, such as in Cases 1 and 4, usually have poorly localized disease. Their brains have not accommodated to the infection and will be edematous and necrotic causing these patients to exhibit significant pressure signs and symptoms. Pressure symptoms are less prominent in many cases of chronic intracranial aspergillosis infection. It is obvious that the total clinical picture will reflect both the pathologic changes occurring as well as their location in the brain. A stroke-like picture may be seen with vascular involvement whereas progressive focal deficits often predominate in cases with well-localized masses. Often the intracerebral location of these masses will point to the primary focus of extracranial infection. Unusual presentations include unilateral exophthalmos15,28 and trigeminal involvement.27,32 Although fever may occur in these patients, it has been unusual in reported cases.

If examined, the spinal fluid usually shows moderate protein elevation, usually above 100 mg%, a normal glucose and a variable pleocytosis. The cellular response usually is neutrophilic with marked elevations seen in cases complicated by meningitis. When hemorrhage or vascular invasion occurs, red cells may predominate in the spinal fluid.32 Pressure may be normal or elevated. Culture of cerebrospinal fluid has only rarely yielded growth of aspergillus. Tests of the spinal fluid for aspergillus precipitins have not been reported.

Non invasive ancillary tests may be useful. Serologic demonstration of aspergillus precipitins has not been employed specifically in patients with cerebral aspergillosis. Its use in patients with extracranial aspergillus infections suggests that only a positive result is significant, for the incidence of false negative results is high.23 Electroencephalography may point to focal disease, but in many cases of cerebral aspergillosis it may only indicate diffuse cerebral dysfunction.23 Plain roentgenograms of the skull rarely may demonstrate calcification of a nonspecific nature in aspergillus granulomas.14 Radionuclide brain scanning has identified focal disease not only in our patients but in others reported in the literature.19, 20,24,30 However, our experience with Case 1 indicates that the differentiation between discrete granulomas or abscesses as opposed to foci of cerebritis may not be possible with brain scanning. Experience with cerebral parenchymal infections of different etiologies indicates that smaller areas of infection may not be seen with brain scanning.7 This may detract from its usefulness in cerebral aspergillosis, a disease often associated with multiple small foci of infection as seen in two of our cases. A brain scan showing multiple lesions may suggest metastatic cancer, a setting associated with aspergillosis; the inability of the scan to predict histology in this circumstance is a drawback. Negative brain scans should not deter further investigation, as a false negative scan has been noted in cerebral aspergillosis abscess.23 Although it may prove valuable, the computerized transaxial tomographic technique has not yet been reported in this disease.
specific nature of these changes argues for considering the invasive neuroradiologic tests as complementing the brain scan in diagnosing intracranial parenchymal infections.16

Treatment of varying forms of cerebral aspergillosis has been almost uniformly disappointing. Hendrick and Conen have reported what appears to be the only survivor from removal of a cerebral aspergillus abscess.12 Peet had earlier reported an operative survivor but Cawley later reported autopsy results on this patient.5 Tveten et al document a patient who succumbed to recurrent aspergilloma ten years after undergoing operation for intracranial extension of a primarily intraorbital granuloma.28

Our cases point out the difficulties of manipulative treatment. The first case had evidence of several foci of involvement. Closed biopsy technique succeeded in obtaining diagnostic tissue which may have been the guide for antifungal therapy with amphotericin B had the patient lived longer. However needle biopsy did not provide a means of decompressing the acutely swollen brain of this patient. Had a true abscess cavity rather than a focal area of cerebritis been encountered, decompression may have been accomplished with closed biopsy. In this acute setting, the only form of decompression available would have been lobectomy or large craniectomy with the understanding that significant amounts of involved tissue would remain in situ.

Our second patient had a chronic process with little, if any, acute brain reaction to the mass lesion. Lobectomy afforded both decompression and almost complete removal of infected tissue from the area explored. A twenty-four hour delay in starting intrathecal amphotericin B may have contributed to the fungal meningitis found at autopsy. It may even be advisable to irrigate the manipulated area with amphotericin B in the operating room and provide an avenue

for postoperative chemotherapy to this area by placing a reservoir in the subarachnoid space around the lesion. The intrathecal route may not be as effective in this condition, for these infections are often associated with meningeal reaction causing secondary obstruction to the cerebrospinal fluid circulation. Neurosurgical treatment of intracranial tuberculomas has shown that preoperative treatment with antituberculous agents may significantly lower the previously high postoperative incidence of tuberculous meningitis.13 Applying this experience to intracranial aspergillus infections, we would advocate initiating antifungal therapy with amphotericin B in the preoperative period to a planned total dose of 3.0 gm over six weeks in patients with 1) extracranial foci of infection amenable to sampling of tissue for staining and/or culture of organisms; 2) selected patients whose clinical setting and the preoperative assessment of the intracranial lesion, make aspergillosis infection likely. In spite of the generally poor results achieved with amphotericin B in neurological aspergillus infections,20 we believe that trials of this potent agent as an adjunct to operation are indicated in view of the disappointing surgical results, not only in patients who are devastated by their intracranial lesion, but most importantly, in those patients who show minimal alterations in state of consciousness, and have discrete lesions in areas of brain amenable to radical extirpation. We hope to improve the mortality in this latter group of relatively good operative risks by preoperative chemotherapy.

References
CEREBRAL ASPERGILLOSIS

Aspergillus is a fungal organism that can cause disease in humans. The most common sites of infection are the lungs, brain, and skin. Infections of the brain can cause a wide range of symptoms, including headache, fever, and altered mental status. The diagnosis of cerebral aspergillosis is typically made through imaging studies and fungal culture of tissue samples. Treatment options include antifungal medications, surgery, and radiation therapy. The prognosis for patients with cerebral aspergillosis can vary depending on the extent of the infection and the underlying health of the patient.

News Notes

NEURO-OPHTHALMOLOGY COURSE

The faculty of the University of Miami School of Medicine, Department of Ophthalmology, is offering a Course in Neuro-Ophtalmology, January 9-10, 1976, at the Key Biscayne Hotel, 701 Ocean Drive, Key Biscayne, Florida. The Course consists of three parts: A. Neuro-Ophtalmology Symposium; B. Strabismus Symposium; and C. Vitreous-Retinal-Choroidal Symposium. Information: Bascom Palmer Eye Institute, Post-Graduate Education Courses, P. O. Box 520875, Biscayne Annex, Miami, Florida 33152.

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Symposium on the Myelomeningocele Patient—A Multidisciplinary Approach, March 11-13, 1976, University of Cincinnati Medical Center, Cincinnati, Ohio. Focus will be on general problems, with individual workshops in neurosurgery, orthopaedics, urology and allied health professions. For details write to the Office of CONMED, Suite E251, 231 Bethesda Avenue, Cincinnati, Ohio 45267.

ROCKY MOUNTAIN NEUROOPHTHALMOLOGY COURSE

Rocky Mountain Neuroophthalmology Course, Santa Fe, New Mexico. February 5-7, 1976. Coordinator: Dr. Thomas J. Carlow, Department of Neurology, University of New Mexico, 1007 Stanford Drive NE, Albuquerque, New Mexico 97131.

REVIEW COURSE IN NEUROLOGICAL SURGERY

Review Course in Neurological Surgery February 6-15, 1976, at Cook County Graduate School of Medicine, Chicago, Illinois. The course is designed to provide an intensive, comprehensive review of the disciplines essential to the neurological surgeon. The course should serve as a base from which candidates for the written or oral Board examinations may proceed with their personal study. Apply to: Cook County Graduate School of Medicine, Inc., 707 South Wood Street, Chicago, Illinois 60612.

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