

Aspergillus infection of the Central Nervous System

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Abstract

Aspergillus fumigatus is the most common human pathogen in the genus *Aspergillus*. Intracranial granulomas, abscesses, and blood vessel invasion are characteristic features of aspergillosis. Presenting features are those of focal neurologic deficits due to intracranial mass lesions. Paranasal sinus or respiratory tract fungal infection is usually concomitant. Aggressive surgical excision combined with systemic antifungal therapy is the mainstay of treatment. Liposomal preparation of amphotericin B offers better penetration of the drug with reduced side effects. The prognosis for central nervous system aspergillosis is poor and the disease is usually fatal.

Key words: Aspergilloma, brain, fungi, amphotericin

Introduction

The word fungus has an interesting etymology, being *sfungus* = sponge, one with many pores. Homer's *Odyssey* (1050-850 B.C.) refers to the 'many-pored sponges'. So, porous, sporous, spongous, *sfungus*, fungus. The white mold on your brown bread is porous and foretells you of the porosity of the bread that is fungal in origin. The science of fungi isn't fungology but mycology, from Gk. *mycos* = fungus or mushroom. The science of mycology dates back to 1677 when Hooke, a contemporary of Newton and the first to microscopically describe and name a 'cell', discovered that the yellow spots on rose-leaves consisted of filamentous fungi, the study of which he started. Saccardo, in 1906, published an 18-volume *Sylloge fungorum*, carrying an account of 57,660 fungi, a figure crossing 150,000 as of today. The whole antibiotic era started with the fungus *Penicillium notatum* that favored Fleming, Florey and Chain with a Nobel prize.

Fungi are common in the environment, but only a few are pathogenic. In general fungi are organisms of low pathogenicity, emerging as opportunistic organisms thriving in a compromised host, however some will infect

even normal hosts. Aspergillosis is an infection of tissues or cavities by fungi of the genus *Aspergillus*. In the nervous system, the infection can be found in the cerebral parenchyma, the meninges or the vascular system.

Fungal infections of the central nervous system (CNS) are almost always a clinical surprise. Their presentation is subtle, often without any diagnostic characteristics, and they are frequently mistaken for tuberculous meningitis, pyogenic abscess, or brain tumor. Granulocytopenia, cellular and humoral mediated immune dysfunction are predisposing factors to the development of CNS infections in immunosuppressed patients. Only with a high index of suspicion, an aggressive approach to diagnosis, and rapid vigorous therapy may we hope to alter the clinical course in this group of patients.¹

Intracranial fungal infections are being identified more frequently due to the increased incidence of auto-immune deficiency syndrome (AIDS) patients, better radiological investigations, more sensitive microbiological techniques, and better critical care of moribund patients. General awareness of the possibility of fungal infection has also increased.

Disseminated aspergillosis is more common in an immunocompromised host as an opportunistic infection as seen in acquired immune deficiency syndrome (AIDS). CNS aspergillosis is also seen in cardiac, renal and other organ transplantation patients. It is also

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noted in neutropenia associated with acute leukemia and its therapy, and patients of glioblastoma multiforme on steroid therapy.¹

The Organism

Aspergillus fumigatus is the most common human pathogen in the genus *Aspergillus*, but *A. flavus*, *A. niger*, and *A. oxyzae* are also frequently seen. They have worldwide distribution. *Aspergillus* are saprophytic opportunistic ubiquitous fungi found in soil, plants and grows as a mold on decaying vegetable matter. It has branching septate hyphae varying from 4 to 12 microns in width, which show dichotomous branching and produces numerous spores on the tips of long conidiophores.²

Aspergillus fungal spores are commensal in the respiratory tract and external auditory canal. Maxillary sinusitis of dental origin or the lungs are the most common sites of primary *Aspergillus* infection. The primary portal of entry for *Aspergillo*sis organisms is the respiratory tract. Infection reaches the brain directly from the nasal sinuses via vascular channels or is blood borne from the lungs and gastrointestinal tract. Rarely the infection may also be air borne contaminating the operative field during a neurosurgical procedure.³ CNS infection has also occurred as a complication of pituitary surgery.⁴

Neuropathology

Intracranial infection spread of *Aspergillus* infection occurs more frequently through the hematogenous route and less frequently through direct or contiguous spread. Direct extension from the sinuses or orbit has been reported. Dissemination of the *Aspergillus* fungi to the brain from a pulmonary source occurs in 10% of patients. Direct infiltration into the basal bones leads to the more commonly encountered skull base osteomyelitis. Intracranial infection can affect the parenchyma or the meninges. According to the site and nature of infection, the patient may present with features of meningitis, focal neurological signs or symptoms of raised intracranial pressure. The cerebral vasculature can be involved by mycotic aneurysms or intra-arterial thrombosis. *Aspergillus* hyphae can invade directly into the

vessel wall which becomes weakened due to necrosis and polymorphonuclear infiltration, resulting in mycotic aneurysm formation. These patients may present with typical subarachnoid hemorrhage syndrome. Intraluminal extension of the hyphae can also initiate thrombus formation. Rarely, major arterial stenosis may occur following leptomenigeal infection. Steroids can inhibit the macrophage response to intracellular fungus and may permit enhanced germination.

Single or multiple abscess formation with blood vessel invasion leading to thrombosis is a characteristic feature of *Aspergillo*sis on neuropathologic examination. *Aspergillus* has a marked tendency to invade arteries and veins (angiotropic) producing a necrotizing angitis, secondary thrombosis, and hemorrhage. Onset of cerebral *aspergillo*sis is heralded by manifestations of focal neurologic deficits in the anterior and middle cerebral arterial distributions. The evolving hemorrhagic infarcts convert into septic infarcts with associated abscesses and cerebritis. The fungal hyphae are found in large, intermediate and small blood vessels with invasion through vascular walls into adjacent tissue; invasion in the reverse direction can also occur. Purulent lesions may be chronic and have a tendency toward fibrosis and granuloma formation. Microscopically the most striking feature is the intensity of the vascular invasion with thrombosis. In purulent lesions, pus is seen in the center of the abscesses with abundant polymorphs at the periphery. Granulomas consist of lymphocytes, plasma cells and fungal hyphae.⁵

Clinical manifestations

*Aspergillo*sis should be considered in cases manifesting with acute onset of focal neurologic deficits resulting from a suspected vascular or space-occupying lesion especially in immunocompromised hosts. In patients with paranasal sinus disease, orbital extension with proptosis, ocular palsies, visual deterioration, and chemosis may occur. The symptoms frequently encountered are headache, vomiting, convulsions, hemiparesis, fever, cranial nerve deficits, paralysis and sensory impairment of varying degree. Features typical of meningitis

and subarachnoid hemorrhage resulting from mycotic aneurysms may manifest.^{1,2,5}

Patients are often afebrile or have only a low-grade fever. Their symptoms are usually those of a cerebral mass lesion, although the propensity of the fungus to invade blood vessels may lead to extensive necrosis and sometimes to intracranial bleeding.⁶

The disease is usually slowly progressive and symptoms may persist for months. Brainstem or cerebellar signs were the presenting features in one series of 11 patients, in which rapid neurologic deterioration and death occurred in 9.¹

Goel *et al*⁷ have reported aspergilloma to involve the Gasserian ganglion in two healthy individuals. These paracavernous tumors mimicked a meningioma and a trigeminal neurinoma on preoperative imaging and intraoperative consistency and vascularity. The lesions were successfully and completely resected. Both patients developed major cerebral arterial territory infarcts in the postoperative phase, remote from the site of the operation, leading to crippling neurological deficits in one patient and death in the other. Nadkarni *et al*⁸ have reported a similar clinical course in a 32-year-old male with paranasal sinus infection with intracranial extension. This patient succumbed to a basilar artery thrombosis following a left frontal granuloma excision (Fig.1). These cases highlight the unusual location of intracranial aspergilloma and the possibility of ischaemic complications after surgical resection of intracranial aspergilloma.

Of the 73 patients treated for fungal infection between 1967 till date in our Institution, 22 patients had a histological confirmation of the diagnosis of CNS aspergillosis. There were 14 males and 8 females in this group and their age ranged from 20 to 58 years (average 44 years). Three patients tested positive for human immunodeficiency virus infection. Four patients had diabetes mellitus. The lesion in four cases was in the proximity of cavernous sinus. In one case, the lesion was within the dural confines of the Meckel's cave and extended in a plexiform manner along the second division of the trigeminal nerve. In another case the extensive basal lesion involved the paranasal sinuses, orbit, cavernous sinus and the medial temporal brain. In rest of the eighteen cases, the lesion was located within the cerebral hemisphere and presented as a large mass with extensive cerebral edema. All 22 patients succumbed to their disease within one year of diagnosis. Autopsy was performed on 14 of these patients as they died during their hospital stay within ten days of surgery. Twelve of these patients harbored aspergillus granulomas with abscesses. The brain showed evidence of meningitis and generalized cerebral edema. The intracranial vasculature in 3 of these patients showed aspergillus invasion and secondary thrombosis. One patient had been operated for cavernous sinus aspergillus granulomas. This patient died postoperatively after developing arteritis and an infarct distal to the site of surgery. Autopsy examination confirmed that fungal arteritis that led to the cerebral infarcts. Another patient had a basilar artery thrombosis and a massive posterior circulation infarction in the post-

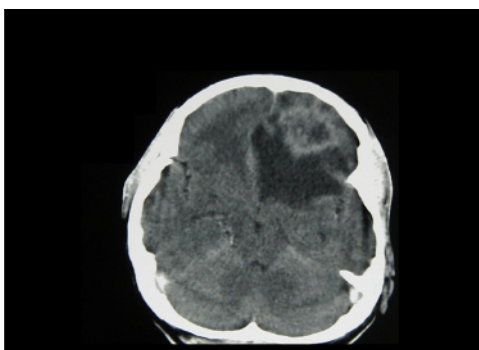


Fig 1A. Post-contrast axial Computed tomography (CT) scan shows a left frontal aspergillus granuloma

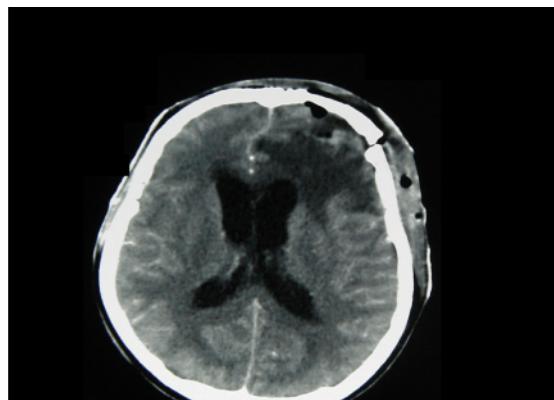


Fig 1B. Postoperative CT scan shows excision of left frontal granuloma by a left frontal craniotomy

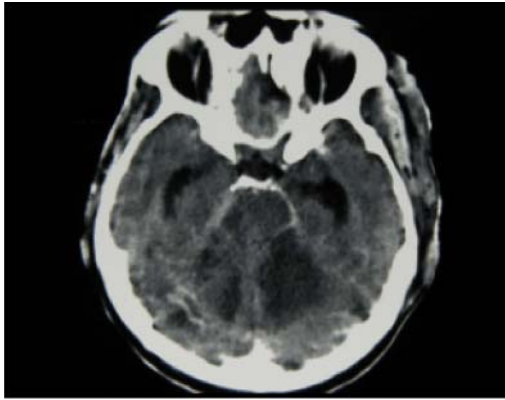


Fig 1C. Postoperative CT scan shows bilateral cerebellar and brainstem infarcts noted as hypointense areas.

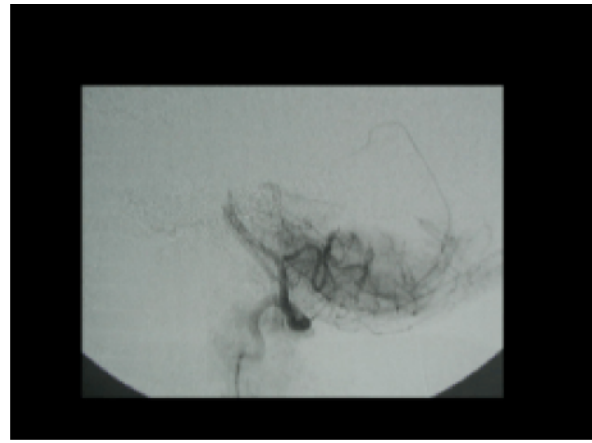


Fig 1D. Vertebral angiogram demonstrates complete occlusion of basilar artery.



Fig 1E. Axial cut section of the post-mortem specimen of the brain shows a brainstem infarct.

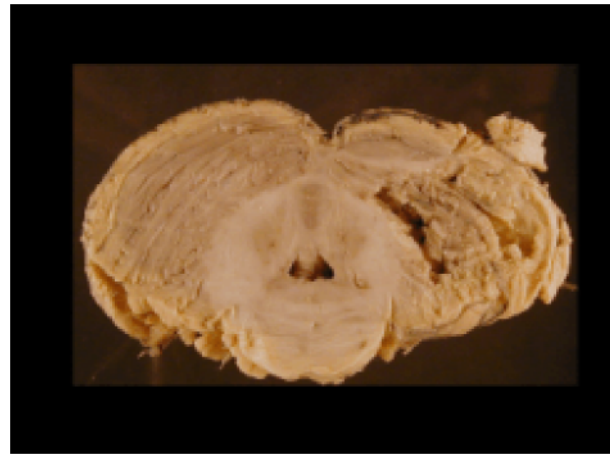


Fig 1F. A section taken inferiorly shows a cerebellar infarct

operative phase(Fig.1) . Autopsy study and examination of the basilar artery confirmed presence of aspergillus fungus within the artery and thrombosis of the vessel.

Investigations

Spinal fluid findings

In general, lumbar puncture is contraindicated in patients with intracranial mass lesions associated cerebral edema. Altering the intracranial pressure by withdrawing spinal fluid for laboratory examination may precipitate a cerebral herniation syndrome or abscess rupture into the ventricular system.

Spinal fluid pleocytosis (600 cells/mm³) and moderately elevated CSF proteins are present, but CSF glucose is usually normal in CNS Aspergillosis. There are many exceptions to this

picture and virtually any CSF response can occasionally be seen, including a normal spinal fluid. Organisms are rarely found in CSF. The characteristic branching separate hyphae and conidia of *Aspergillus* species are faintly visible with H & E stain and periodic acid-Schiff (PAS) but are most readily seen with Gomri's methenamine silver (GMS) stains. Potassium hydroxide wet preparations can demonstrate *Aspergillus*. Red blood cells may be seen in the CSF of patients with CNS aspergillosis.^{1,2}

Neuroradiology (Figs.2 and 3)

Diagnosis of an intracranial mass lesion is best confirmed with a computed tomography (CT) or magnetic resonance (MR) imaging of the head with or without intravenous contrast. On CT low density lesions that may or may not enhance with contrast can represent fungal

abscesses. Chronic abscesses have demonstrated ring and homogenous enhancement. Minimal mass effect, low absorption areas, and slight or

no contrast enhancement were seen on CT in patients with *A. fumigatus* brain abscess. The increased sensitivity of the MR imaging scan can

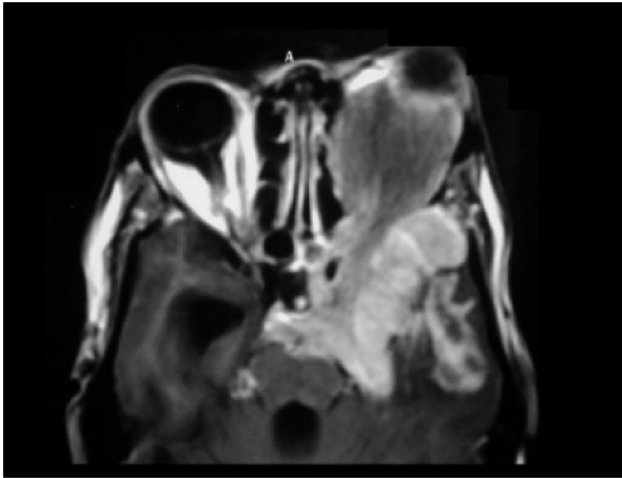


Figure 2A. Post-Gadolinium magnetic resonance (MR) axial image that shows an enhancing mass extending from the orbit into the cranium. The mass invades into the ethmoid sinuses, cavernous sinus, sphenoid sinus, and middle cranial fossa. The internal carotid and basilar arteries are encased in the inflammatory tumor. The temporal brain has been infiltrated.

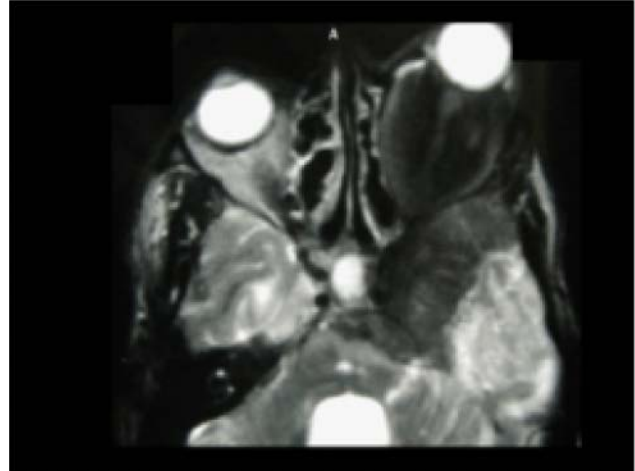


Figure 2 B. T2-weighted axial MR image shows that the mass is hypointense, typical of an inflammatory granuloma. Histologically this tumor was an aspergilloma

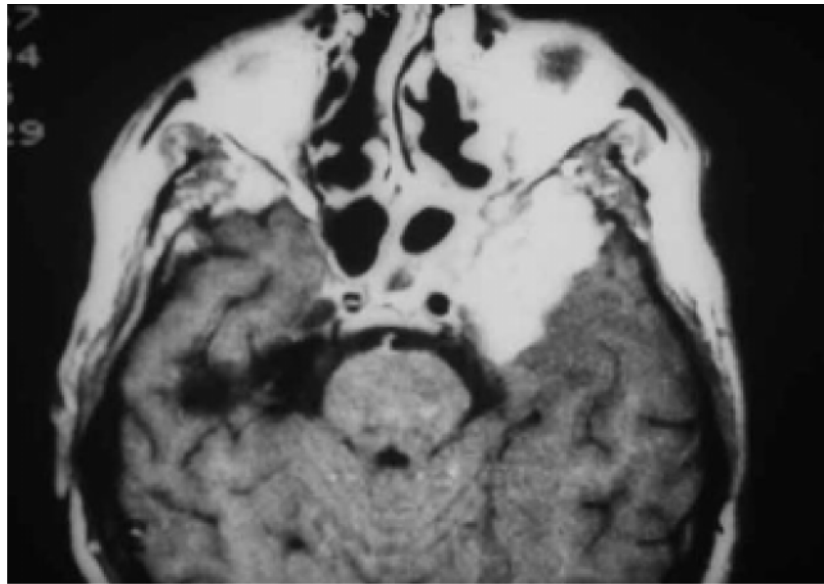


Figure 3 Post-Gadolinium magnetic resonance (MR) axial image shows an enhancing cavernous sinus mass. The mucosa of the sphenoid and ethmoid sinuses are thickened and enhancing. Histology confirmed the mass to be an aspergilloma

be useful for demonstrating multiple small intracerebral abscesses not apparent on CT. CT scanning also provides a convenient way to monitor a patient's response to anti-microbial therapy.

Culture

Aspergillus cultured optimally on Sabourad's agar demonstrates characteristic conidiophores. However, blood and cerebrospinal fluid cultures, even in disseminated disease are frequently negative.

Serologic Tests

Serial serologic tests (i.e. double diffusion counter immunoelectrophoresis, immunofluorescence, or enzyme-linked immunosorbent assay) significantly help in arriving at a diagnosis. Immunoassay may detect the disease early but these tests are rarely done. Serologic testing has been unreliable for *A. fumigatus*, except in leukemia patients followed prospectively.

Therapy

Surgical excision enhances abscess penetration by removal of necrotic debris.

Radical surgical debridement can be curative in aspergillus brain abscess if the extent of resection extends into uninvolved tissue. Lobectomy in patients with a single *A. fumigatus* abscess is an acceptable surgical option when non eloquent areas of the brain are involved. In four of seven patients with cerebral aspergillosis who survived, complete surgical resection of brain abscess was accomplished.⁹ Aggressive neurosurgical intervention for surgical removal of *Aspergillus* abscesses, granulomas, and focally infarcted brain; correction of underlying risk factors; amphotericin B combined with flucytosine and treatment of the source of infection should form the mainstay of the management.

The ischaemic complications after surgical resection of intracranial Aspergillomas are well documented.^{7,8} The postoperative phase of patients operated for aspergillus infections of the brain is marred by major cerebral arterial territory infarcts remote from the site of infection, leading to crippling neurological deficits and even death. Histological infection

has shown fungal hyphae within the wall of the involved arteries. The stress of surgery and the use of steroids to control cerebral edema in the immediate postoperative phase may have been contributory factors in the fungal growth. High awareness of the possibilities of fungal infection on the basis of radiology or operative findings, avoidance of steroids, and early treatment with antifungal agents may help avoid such a vascular insult.

Stereotactic aspiration is the procedure of choice for most brain abscesses, particularly those measuring more than 1.5 cm. Indications for aspiration include to aid in diagnosis, to relieve mass effect, to improve the efficacy of drug treatment, and when systemic therapy appears to be ineffective for a presumed organism. Complete aspiration of an abscess is not necessary and can predispose to hemorrhage into the evacuation cavity. Stereotactic drainage or biopsy and systemic, intraventricular or intraocular administration of amphotericin B has been effective in *Aspergillus* abscesses.¹

Amphotericin B has been the mainstay of therapy for the past quarter century. Combination therapy with 5-fluorocytosine has also been recommended.

Rifampin and 5-fluorocytosine may act synergistically with amphotericin B when treating CNS fungal disease. Itraconazole, miconazole and sulfamethoxazole have also been effective. Because of poor penetration into the CSF when given systemically, direct instillation of amphotericin B into an abscess cavity through an indwelling catheter has been advocated.¹⁰ To reduce the toxicity of amphotericin B, liposomal amphotericin B and its combination with lipids have been introduced. Liposomal amphotericin B (FungisomeTM) has been demonstrated to be safe and efficacious in treatment of CNS aspergilloma.^{11,12,13} This indigenous preparation is significantly cost effective when compared to other similar preparations.

Whenever possible, immunosuppressive therapy should be lowered or discontinued in the compromised host with CNS infection. Unfortunately, rejection is often concomitant with infection, requiring higher doses of

immunosuppressive agents. In patients with cancer, systemic disease is frequently stable because of continuing chemotherapy administration when CNS infection develops.

Prognosis

The prognosis for central nervous system aspergillosis is poor, with most reported cases being fatal. Fungal abscesses in patients with cancer are usually fatal.¹⁴ An aggressive surgical approach in non-immunocompromised patients helped reduce the mortality from 64% to 39%.¹⁵ Intracerebral aspergillosis is frequently fatal in immunocompromised patients, with only 12 reported cases of successful treatment.¹⁰

Because many immunocompromised patients have had years of productive life before developing CNS infection, rapid diagnosis and effective medical and surgical treatments are essential to preserve neurologic function and assure a good quality of life.

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