CASE PEPORT

# CNS Aspergillosis

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ABSTRACT

Cerebral aspergillosis has the tendency to occur in immune-compromised patients. Less commonly, immune-competent individuals can be affected, with neuroimaging findings being difficult to interpret. A surgical excision with aggressive antifungal therapy is required for a proper management. This case report describes an immune-competent patient with cerebral aspergillosis that presented radiologically as a suspicious mass to be diagnosed pathologically and excised surgically.

**Key words:** Cerebral Aspergillosis, CNS fungal infection, antifungal.

## Introduction

CNS infections are not uncommon in a developing country like Bangladesh with huge population burden, poor hygiene, malnutrition and less health awareness. A retrospective study conducted by the Department of Neuropathology at NINS&H for a period of five (05) years between June 2013 to March 2018 involved a total of 2504 intracranial SOL cases of which 61(2.4%) cases were infectious lesions. Among 61 cases, 33(54.1%) cases were tubercular, 21(34.4%) cases were suppurative and rest 7(11.5%) cases were fungal.[1] Cerebral aspergillosis has the tendency to occur in immune-compromised patients. Less commonly, immune-competent individuals can be affected, with neuroimaging findings being difficult to interpret. The diagnosis necessitates imaging of the brain as well as the sinuses with biopsy and pathological confirmation. A surgical excision with aggressive antifungal therapy is required for a proper management. This case report describes an immune-competent patient with cerebral aspergillosis that presented radiologically as a suspicious mass to be diagnosed pathologically and excised surgically.

## Case Report

A 42-year male non-diabetic, normotensive, non-asthmatic poultry farmer was admitted to the hospital with history of weakness in right upper and lower limbs, dysphasia and episodes of absence seizure for 2 years. His weakness initially was on the right upper limb which was insidious in onset, progressively increased making him unable to perform day to day activities with loss of grip. His condition gradually deteriorated and developed right-sided hemiparesis and aphasia for the last 12 months. He had no history of headache, loss of consciousness but had few episodes of absence seizures. On examination, his higher psychic function was normal. His cranial nerves were intact. His pupils were equal on both sides, 3mm in diameter, regular, reacting to light. He exhibited motor deficit on the right side, MRC grading 2/5. No sensory deficit, signs of cerebellar dysfunction or meningeal irritation were present. On investigations, FBC showed Neutrophilic leukocytosis. The Chest X- ray was normal. The serological test of the patient for HIV and HBV were negative. CT- scan of Brain showed a single rim

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contrast enhancing hypodense area with surrounding edema in left fronto-parietal region with slight mid-line shift to the right (Figure 2). Provisional diagnosis was Tuberculoma. The differential diagnoses were High grade glioma, pyogenic abscess and metastasis. For our patient, post-operative period was uneventful. Post-operative CT-scan of Brain immediately after surgery (Figure 3.1) showed edematous changes containing air densities in left fronto-parietal white matter. CT scan at the end of 3 weeks after operation showed no new lesion in the left fronto-parietal region [Figure 3.2]. Follow-up at 8 weeks as well as 6 month (Figure 4.1, 4.2) after operation revealed hypo-intense mass with hyper-intense thin rim in left fronto-parietal region in MRI scan. Patient's right-sided hemiparesis and aphasia improved. After taking Voriconazole for 12 months, the patient presented with Drug-induced cholestasis which was managed by lowering the dose of voriconazole. Within the duration of 22 months after discharge, he had 2 episodes of seizures 6 months apart. He is also receiving Levetiracetam 500mg thrice daily since the beginning. He is co-operative and conscious, under follow-up.

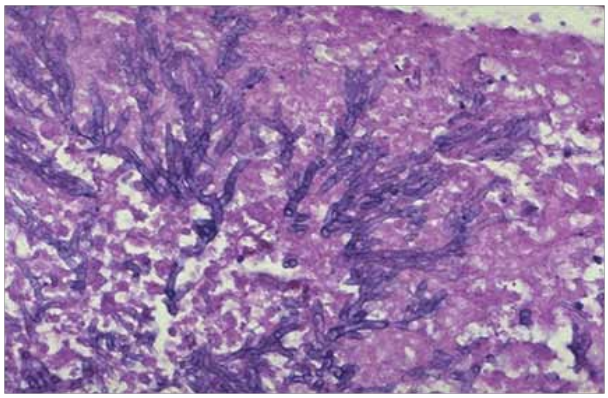

**Figure 1:** Fungal hyphae with spores on Histopathology (H&E preparation).

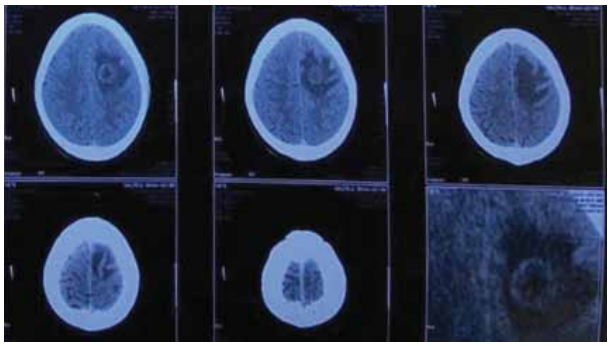

**Figure 2:** CT-scan of Brain with contrast- Single rim enhancing hypodense lesion in the left fronto-parietal region with peri-lesional edema.

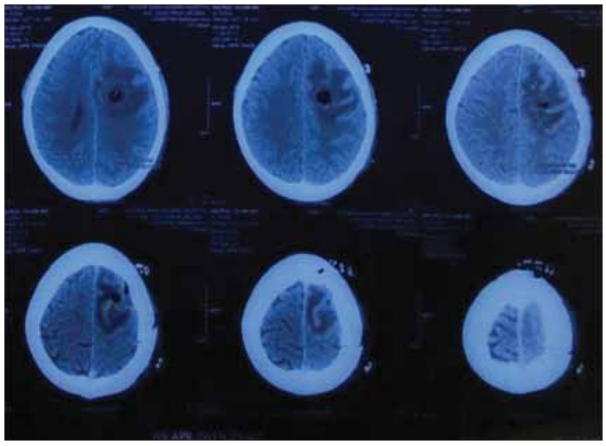

**Figure 3.1:** CT-scan of Brain (08 Apr 2019) showing edematous changes containing ai densities in left fronto-parietal region.

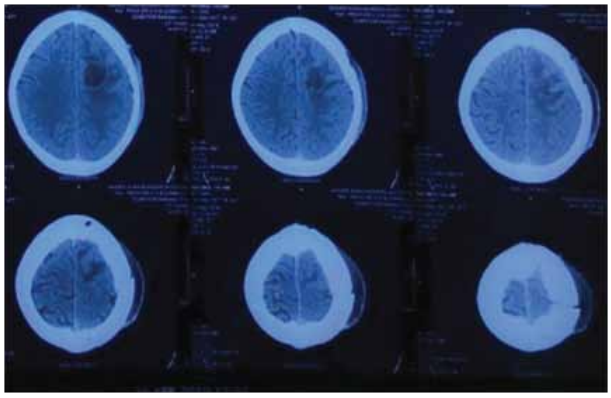

**Figure 3.2:** CT-scan of Brain (30 Apr 2019) showing similar findings as fig. 3.1.

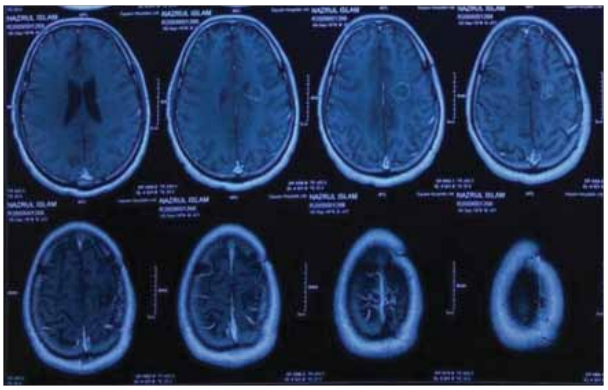

**Figure 4.1:** Axial T1-weighted MR image showing ring enhanced hypo-to-isotense lesion in left fronto-parietal region.

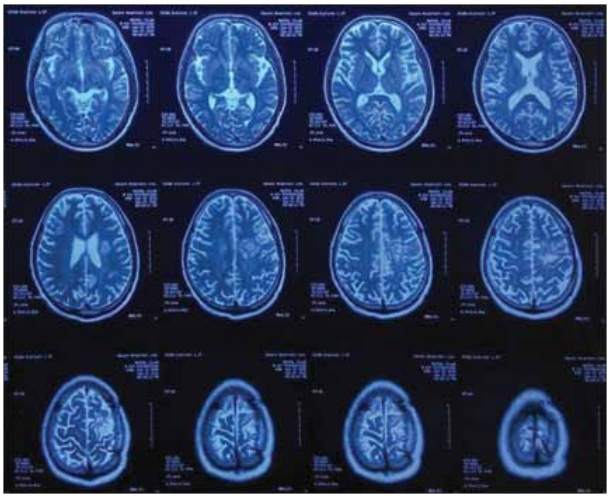

**Figure 4.2:** Axial T2-weighted MR image showing ring enhanced hyperintense lesion with surrounding edema in left fronto-parietal region.

**Discussion:**

As the study mentioned above, incase of fungal infection(7 cases) highest incidence was of aspergillosis(4 cases) followed by zygomycosis(2 cases) and phaohypomycosis (1 case). CNS aspergillosis results from angioinvasive infection of the central nervous system by the fungus Aspergillus spp.[2] The clinical manifestations and prognosis of CNS aspergillosis are distinctly different in immune-competent and immune-compromised patients. The mortality rate of Aspergillus infection in the immune-competent population is approximately 10% to 20%, while that in immune-compromised patients can be as high as 85% to 100%. In immune-compromised patients, a clear history of immune abnormalities is usually noted and the Aspergillus often invades multiple sites. Whereas, in immune-competent patients it usually manifests as isolated brain lesions that present a great diagnostic challenge.Aspergillus infection in the CNS is relatively rare and is frequently misdiagnosed and undertreated in the immune-competent population. The clinico-radiological features of CNS aspergillosis have not been well elucidated, and the clinical treatment remains challenging in immune-competent patients. Mortality in patients treated with voriconazole is still unacceptably high, and more efficacious treatments are needed.[3]

There are more than 200 species of Aspergillus but fewer than 20 have been implicated in human disease; the most important are A. fumigatus and A. flavus. Aspergillus species are ubiquitous in the environment, growing in the soil, on plants, and on decomposing organic matter.[4] The lungs are the primary site of infection because Aspergillus tends to enter the human body in the form of spores by inhalation. CNS infection may occur through different ways[4,5,6]

I. Hematogenous dissemination from the lungs.

II. Direct extension from the paranasal sinuses, ear and orbits.

III. Direct inoculation at the time of neurosurgery.

IV. Traumatic implantation of spores in corneal infection.

V. Inadvertent inoculation as in endocarditis.

VI. Introduction of foreign bodies in the form of ventriculoperitoneal shunts and Ommaya reservoirs.

VII. Performance of Lumbar punctures and injection of drugs.

VIII. Head trauma.

Major risk factors predisposing to CNS aspergillosis include hematologic malignancies, allogeneic bone marrow transplantation, hematopoietic stem cell transplantation, solid organ transplantation, the acquired immunodeficiency syndrome, chronic pulmonary diseases, use of immunomodulating drugs, such as alemtuzumab, chemotherapy, corticosteroids. Other identified risk factors have included hepatic failure, Diabetes mellitus, Cushing's syndrome, and thermal burns.[6] Different from other cases of immune-competent hosts presented in the literature, our patient had no diabetes mellitus, prolonged hospitalization, or malignant disease. However, he had a history of working in poultry farm as a possible predisposing factors for the development of nasal aspergillosis followed by spread to the brain.

CNS manifestations of intracranial aspergillosis include intracranial aneurysms, meningitis, infarction, hemorrhage, single or multiple cerebral abscesses (most common), epidural abscess or myelitis or mycotic aneurysms and space-occupying granulomas.

Occlusion of intracranial vessels ensues with consequent infarction of tissue and subsequent abscess formation.[6] The most common finding is a mass lesion with a thick irregular wall, which indicates a competent host defense mechanism that is attempting to encapsulate or isolate the offending organisms.[7] Cerebral aspergillosis predominantly affects intra-axial structures, although adjacent tissues such as meninges can also be involved. Arterial route is the main route of contamination and the disposition of intracerebral arterial division causes development of diseases in this way at the in transitional zones between cortex and white matter, and are characterized by gray discoloration and softening of the central tissue.[6] Branches of the middle and anterior cerebral arteries are usually infiltrated by hyphae, resulting in direct or indirect damage, especially in frontal, temporal, and parietal lobes. Deep cerebral nuclei and white-matter tracts can also be involved, but damage to cerebellar lobes and further structures of the posterior fossa is scant. Hemorrhages in some lesions make them darker and harder. The surrounding tissue is often edematous. Meningeal involvement may appear as opacity and thickening of the meninges, related to invasion by inflammatory cells and surrounding fibrosis.[9]

Clinical presentations are similar to those in neoplasms, making diagnosis problematic. The most common symptoms involved focal neurologic deficits, and it depends on the region affected. Convulsions, fever, hemiparesis, cranial nerve deficits, paralysis, and sensory impairment are common. Features of meningitis and subarachnoid hemorrhage resulting from mycotic aneurysms also have been reported in the literature.[7] In our review focusing on immune-competent host presented with space-occupying lesions, the most common symptom was hemiparesis and aphasia.

The diagnosis of CNS aspergillosis requires the demonstration of the organism and its invasion in CNS tissue or isolation of the organism from a biopsy specimen or CSF. Histologically the granulomas show dense fibrosis with infiltration of lymphocytes, plasma cells, and mononuclear cells along with areas of necrosis which is concordant with the result of our patient.[18] The multi-nucleated giant cells are foreign body type and contain slender septate, acute angle branching hyphae of Aspergillus spp. are best seen after staining with H&E, PAS stain or Gomori'smethenamine silver stain.[17] Also H&E stain helps differentiate aspergilloma and tuberculoma.[18] Staining of brain tissue sample was not performed in our case as it was not advised by the pathologist. Blood cultures in SDA media are rarely positive. Direct microscopy stained with KOH and calcofluor white is often negative. CT or MRI of the brain most commonly shows single or multiple ring-enhancing lesions with surrounding edema. Other radiographic appearances include hemorrhagic infarction pattern, parenchymal hemorrhage pattern, and diffuse necrotic encephalitis pattern. An ELISA and LAT for detecting Aspergillusgalactomannan, an Aspergillus antigen, has been licensed in the United States for the diagnosis of invasive aspergillosis.[8]

Immune status is crucial to determine the clinical outcomes.[7] A combined medical and neurosurgical treatment should be considered in all patients with this disease.[10] The prognosis for cerebral aspergilloma is generally poor, although surgical removal and drainage may give temporary improvement, and sometimes cure, particularly when coupled with administration of anti-mycotic agents. Amphotericin B has been regarded generally as the drug of choice for effective therapy, although in recent years the azoles have been tried, being less toxic and more acceptable to the patient.[11] The major causes for the devastating prognosis in CNS aspergillosis are limited number of drugs, toxicity of the drugs and a poor penetration of antifungal drugs into the CNS, with the exception of voriconazole. Treatment with voriconazole results in measurable drug levels in the cerebrospinal fluid, which may exceed the minimal inhibitory concentration for aspergillus. Moreover, voriconazole brain tissue levels exceed those measured for other antifungal drugs.[12] The following antifungal agents are active against Aspergillus species: amphotericin B deoxycholate, liposomal amphotericin B, itraconazole, voriconazole, and caspofungin. Voriconazole is considered as the agent of first choice for the treatment of invasive aspergillosis. This may also apply for the treatment of CNS aspergillosis. New drugs in development, such

as posaconazole, ravuconazole, micafungin, and anidulafungin are also active against Aspergillus species and may offer new options for therapy. All drugs need to be given at high doses, and the optimal duration of therapy is unknown. Although it would be reasonable to continue to treat until clinical and radiographic abnormalities have resolved, it may be necessary to continue treatment as long as the underlying predisposition for invasive Aspergillus infection exists.[8] Therefore, our patient continues to receive oral voriconazole due to persistence of radiological evidence of infection even after 2 years. Recently published guidelines promulgated by the Infectious Diseases Society of America recommend voriconazole as the primary drug of choice for systemic antifungal therapy of CNS aspergillosis; itraconazole, posaconazole or high dosages of a lipid formulation of amphotericin B are recommended for patients intolerant of or refractory to voriconazole.[6]

Even though Amphotericin B is often used in the treatment of life-threatening fungal infections, impaired renal function is a relatively common complication. As are other renal manifestations, including urinary potassium wasting and hypokalemia, urinary magnesium wasting and hypomagnesemia, metabolic acidosis due to type 1 (or distal) renal tubular acidosis, and polyuria due to nephrogenic diabetes insipidus.[13] Azole antifungals are first-line options in the prophylaxis and prolonged treatment of invasive fungal infections. Long-term use of azoles is associated with hepatotoxicity which was presented by our patient. Other adverse effects include peripheral neuropathies, pancreatitis and hormone-related effects, including gynecomastia, alopecia, decreased libido, oligospermia, azoospermia, impotence, hypokalemia, hyponatremia, and (rarely) adrenal insufficiency. In addition, voriconazole has been associated with periostitis, phototoxic reactions, and squamous cell carcinoma.[14,15]

## Conclusion

CNS aspergillosis usually involves immune-compromised patients; however, immune-competent patients and those with “mild” immunosuppression, such as diabetes mellitus, may also be affected. Our findings indicate that immune-competent subjects are also at risk for Aspergillus infections. CNS involvement often results from dissemination of the infection from the lungs and para-nasal sinuses. A history of prior brain pathology in an immune-compromised patient with IA could be associated with a higher risk of CNS dissemination. Biopsy, CSF culture, and next-generation sequencing are mainstream diagnostic modalities. The combination of antifungal therapy with neurosurgery appears to be the most promising approach. Furthermore, voriconazole is an effective treatment for Aspergillus infection. Early diagnosis and treatment should be highlighted. However, mortality is still unacceptably high, and more efficacious therapeutic approaches are needed.

## Abbreviations

FBC: Full blood count, CNS: central nervous system, SOL: Space-occupying lesion, CSF: cerebrospinal fluid, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus, Spp: Species, IA: invasive aspergillosis, PAS: Periodic acid-schiff, H&E: Hematoxylin and Eosin, CT: computed tomography, MRI: magnetic resonance imaging, ELISA: Enzyme linked immunoassay, LAT: Latex agglutination test.

**Conflict of interest:** none.

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