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Review Article

Craniocerebral Aspergillosis: A review of advances in diagnosis and management

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Abstract

Craniocerebral aspergillosis is a rare but dangerous central nervous system infection. The infection has a spectrum of presenting features, mostly affecting immunocompromised individuals. The incidence appears to be on the rise that has been especially observed in the immunocompetent population. A high index of suspicion, a comprehensive understanding of the infectious process and advanced laboratory and radiological diagnostic techniques, allow early diagnosis. Surgery, followed by systemic anti-fungal medications, remains the cornerstone of management. Early administration of empirical anti-fungal agents along with immunomodulators may further improve prognosis. Immunocompetent patients tend to have better outcomes as compared to those who are immunocompromised. Patients with intradural disease carry the worst prognosis.

Introduction

Aspergillosis disseminating to the central nervous system (CNS), is amongst the most serious sequelae of opportunistic fungal infections. Primary sites of aspergillus infection are the lungs in immunosuppressed and paranasal sinuses in immunocompetent individuals. The CNS may be involved as a primary site, but more commonly it is involved secondarily through haematogenous spread or as a result of direct invasion from adjacent structures. In fact, brain is the second commonest organ to be secondarily affected by invasive aspergillosis. Primary CNS infection may occasionally follow gastrointestinal or skin infections and rarely may occur without a history of an extra cranial source.[1]

CNS aspergillosis has been considered a rare disease, accounting for less than five percent of all CNS infections; although recently there seems to be a rise in their incidence.[2] The reason behind this rise could be the increasing number of immunocompromised individuals due to the growing epidemic of acquired immunodeficiency syndrome (AIDS), chronic granulomatous diseases, autoimmune diseases or due to the rising population of patients having undergone solid organ transplants and consequently on lifelong immunosuppressive therapy. The widespread availability of neuroimaging (CT and MRI) leading to earlier radiological diagnosis in these patients, and thus earlier referrals to neurosurgical centers could also be a contributing factor to the rising incidence. Recently, a peculiar rise in the incidence of craniocerebral fungal infections has been noted in immunocompetent persons, or who have been termed the "apparently immunocompetent" hosts.[3] These cases are unique as they exhibit atypical clinical and radiological features making the diagnosis all the more difficult and causing delay in definitive management. Treatment success is dependent on early diagnosis and aggressive, focused management. This approach has recently lead to relatively encouraging results. The main differential diagnosis of these lesions are brain tumours (both primary and metastatic), intracranial abscesses, and intracranial tuberculomas.

Pathophysiology:

Aspergillus is a ubiquitous fungus in soil, water, decaying vegetation and organic debris, and was recognized to be pathogenic in humans as early as the year 1847. The organism is characterized by spore forming septate hyphae which show dichotomous branching, microscopic findings considered diagnostic for the disease.[4] It also possesses an aerial hyphal stalk harbouring asexually produced conidia, which is the infective form of the organism and is inhaled by the human hosts. This, along with the fact that Aspergillus spores are commensals in the respiratory tract and external auditory canal, makes it understandable that the maxillary sinus and lungs are the most common sites of primary Aspergillus infection.

Among the 19 disease-causing subtypes in the genus Aspergillus, A. fumigatus is the most commonly identified human pathogen, although A. flavus, A. niger and A. oxyzae are also seen. A. flavus has been cultured frequently from immunocompetent hosts and is the commonest cause of fungal sinusitis in these patients.[2] The incidence is especially high in patients from hot and dry areas such as Saudi Arabia, and the Indian subcontinent where it is the most frequently isolated species in cultures of invasive aspergillosis. Once activated, the pathogens may spread to the brain through one of two routes, either invading the cranium directly through the bone; or through haematogenous metastases. Once inside the cranium, the disease may remain entirely extradural, which is the commonest location; or intradural, or it may be present across both sides of the dura. Alternatively, it may just involve the blood vessels or the meninges. The mechanism of damage at the cellular level in cerebral Aspergillus lesions is also complex and and has been shown to be due to secretion

of various necrotizing factors with toxic and lytic activity towards neurons and glial cells. Studies on these toxic factors reveal that A. fumigatus and A. terreus produce small, heat-stable components whereas the toxic activity of A. niger is triggered by a high molecular mass factor which can be inactivated by heat. The active component of A. flavus has a molecular mass similar to that of A. niger but is heat-stable.[5] Secretion of these necrotizing factors might contribute to brain lesions in patients with cerebral aspergillosis.[5]

The clinical manifestations and disease severity are dictated by the immunologic state of the patient. In immunocompromised patients, single or multiple abscesses with marked vascular invasion, with or without thrombosis, is the hallmark of cerebral Aspergillosis on pathologic examination. Aspergillus has a tendency to invade vessels producing a necrotizing angiitis leading to secondary thrombosis with or without haemorrhage. Fungal hyphae are found in large, intermediate and small blood vessels with invasion through vascular walls into adjacent tissue. The large arteries most commonly involved are the anterior and middle cerebral arteries. Evolving haemorrhagic infarcts later convert into septic infarcts with associated abscesses and cerebritis. In immunocompetent hosts, the response differs and a reactive mass forms around the infection in an attempt to limit the spread. This reactive mass is composed of a thick fibrous capsule surrounded by gliotic brain tissue, and may contain within its confines varying consistency of tissues depending upon the state of infection.[5]

In purulent lesions, pus is seen in the centre of the abscesses with abundant polymorphs at the periphery. Purulent lesions can be chronic and may show a tendency towards fibrosis and granuloma formation, consisting of lymphocytes, plasma cells, and fungal hyphae.[5] In summary, brain abscess, epidural abscess, vasculitis and stroke-like illness are manifestations of CNS aspergillosis in the immunocompromised, whereas the immunocompetent generally develop granulomatous masses and meningitis.[6]

Presentation:

The overwhelming bulk of literature on aspergillosis is regarding immunocompromised hosts. Notable case series of craniocerebral aspergillosis occurring in apparently immunocompetent hosts have so far been reported mainly from India, Sudan, Pakistan, Saudi Arabia, UAE, and few other African countries. On the contrary similar publications from West are largely confined to isolated case reports.[2] The reason for this demographic difference is not clear, and a plausible explanation may be the hot, dry climate and low socioeconomic status in the above-mentioned regions, which favour the growth of aspergillus.[2,7]

Classically, craniocerebral aspergillosis should be considered in any patient known or suspected to be immunocompromised, presenting with signs, symptoms and radiological features suggestive of a space-occupying lesion with or without preceding history of nasal blockade and/or discharge. Multiple authors have described a variety of presenting symptoms such as nasal stuffiness, headache, peri-orbital pain, vomiting, convulsions, hemiparesis, cranial nerve deficits (diplopia/ anosmia), proptosis, sensory impairment, dysarthria, lethargy, impaired consciousness, seizures, fever, and rarely, ear discharge.[8] In patients with paranasal sinus disease, orbital extension with proptosis, ophthalmoplegia, visual deterioration (which may lead to total monocular blindness), and chemosis may occur. There are various clinical syndromes associated with fungal infections of the CNS and can involve most part of the neuroaxis.[9] These largely depend on the pathological reaction elicited by the fungus in the host which varies with the virulence of the organism, the antigen makeup of the species and the immune status of the host. They can occur alone or in combination and comprise of meningitis, intracranial mass lesions, skull-base syndrome, rhinocerebral syndrome, stroke syndrome and spinal syndrome. Skull-base syndromes include orbital apex syndrome, cavernous sinus syndrome, proptosis with or without ocular palsy, polyneuritis cranialis and orbito-cranial syndromes. In one study of patients suffering from CNS aspergillosis, 64 out of 89 patients presented with skull base syndromes.[10] The disease is usually slowly progressive and symptoms may persist for months. Alternatively, patients may also present acutely with cerebral infarctions or haemorrhage, a relatively uncommon manifestation of vascular invasion of the fungus.[11] Stroke may also be due to Aspergillus endocarditis leading to embolic stroke.[10]

Laboratory Diagnosis:

Craniocerebral Aspergillosis is difficult to diagnose on laboratory based tests alone as blood cultures and even cerebrospinal fluid (CSF) cultures are frequently negative. Other serologic tests such as double diffusion counter immuno-electrophoresis, immuno-fluorescence, or enzyme-linked immuno-sorbent assay may be helpful in arriving at a diagnosis but are rarely performed. Detection of aspergillus galactomannan, a carbohydrate component of the cell wall of Aspergillus, in urine, CSF or serum, through the above mentioned techniques has moderate accuracy for diagnosis of invasive aspergillosis in immunocompromised patients. The test is more useful in patients who have haematological malignancy or who have undergone haematopoietic cell transplantation.[6] Several authors have attempted to diagnose aspergillosis on the basis of CSF specimen; however, the findings have been inconsistent.[11] Even if the CSF is positive, typically only a small number of fungal cells are present in CSF and a positive culture may only be obtained if a rather

large volume of CSF (preferably 5 milliliters or more) is repeatedly cultured. CSF analysis findings are usually non-specific for fungal disease. These include elevated cell counts, showing pleocytosis, elevated proteins and decreased glucose.[11] Antibody detection in serum or CSF is also not shown to be useful. It has been found that detection of Aspergillus DNA in CSF samples is possible and has the potential to improve diagnosis of cerebral aspergillosis.[12,13] In order to obtain a positive polymerase chain reaction (PCR) result, either fungal cells or fungal deoxyribonucleic acid (DNA) should be present in the CSF sample. Unfortunately, number of cells present in CSF specimen is extremely low, and rate of clearance of DNA from CSF is also unknown. So even if the PCR assay is very sensitive, it still may not be positive. The yield of PCR may be comparatively high in cases of disseminated invasive aspergillosis and cerebral abscesses. However, we do not recommend the use of CSF in the diagnosis of cerebral aspergillosis as obtaining a CSF sample through lumbar puncture in a patient harboring an intracranial space occupying lesion and having raised intracranial pressure may be dangerous. Serologic tests are not considered of much help in reaching a diagnosis; for even a negative result does not exclude the disease. There is also the issue of availability of these tests. These tests may be useful for follow up in patients tested positive prior to intervention (medical or surgical), although in our experience, clinical status alone is a highly reliable indicator of treatment outcome. Whenever possible, diagnosis should be based on a histopathological specimen. A peri-operative squash smear or frozen section seems to us a much better means of identifying the pathology and instituting early pharmacotherapeutic interventions and it is strongly recommended that it be carried out in all patients with suspected aspergillus infection.[14]

Radiological Diagnosis:

The findings in computed tomography (CT) scan and magnetic resonance (MR) imaging are frequently minimal or absent in the hyperacute stage of CNS aspergillosis.[15] Later, there may be multiple irregular lesions with infarction or haemorrhage in a random distribution owing to the angioinvasive nature of the disease.[16] Cerebral aspergillosis basically presents with four principal neuroimaging findings: areas consistent with infarction; ring-enhancing lesions consistent with abscess formation following infarction; dural or vascular infiltration originating from paranasal sinusitis or orbital involvement; and intracranial (intra or extra-axial) space occupying lesions.[17] On CT scanning the lesions are characteristically hyper-dense with mass effect and may or may not show contrast enhancement. Calcifications within the fungal mass may also be present. Abscesses demonstrate ring and homogenous enhancement, mass effect, low absorption areas, and slight or no contrast enhancement. On MR imaging, the classical description is that of an irregular space occupying mass lesion having hypo- to isointense signals on T1-weighted images with either bright homogenous enhancement on post-gadolinium T1 weighted images or ring enhancement pattern. Extremely low signals on T2-weighted images are also frequently seen. The isointensity has been described to be due to coagulative necrosis of brain tissue secondary to fungal involvement of vessels, a finding that has been histologically proven. T2-hypointense zones within the wall of cerebral aspergillus lesions have also been attributed to dense population of aspergillus hyphal elements and the presence of haemorrhage in the capsule but none of the features are specific for intracranial aspergillus infections. Another explanation for the zones of low T2 signal intensity is the presence of iron, manganese, and magnesium in the fungal concretions.[18] This was studied in vitro and a correlation with the concentration of paramagnetic elements within aspergillus colonies and intensity of signals was found.[19] The paramagnetic elements are essential for the hyphal growth, especially iron and magnesium. Also, aspergillus abscesses have been shown to contain a dense population of hyphal elements at the periphery, compared to a relative paucity of fungal elements at the centre, features that likely contribute to the distinct peripheral T2 hypo intensity.[20] The presence of a hypo intense ring in immunocompromised patients has been associated with increased risk for haemorrhage, which occurs in roughly 25% of lesions.[21] The MR imaging finding of a low signal intensity zone surrounded by a thick perimeter of enhancement should suggest the diagnosis of a fungal granuloma caused by the hyphal form of the organism. The thick irregular wall of the mass on MR images indicates a competent host defense mechanism that is attempting to isolate or encapsulate the offending organisms.

Recently, diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy features of CNS aspergillosis have been presented.[22] A high DWI signal character can be present in septic lesions and this finding can be explained by the contents of the abscess cavity. Fungal abscesses exhibit centrally restricted diffusion due to inflammatory cells, necrotic tissue and protein rich exudates.[16] However, in the case of a small lesion without contrast enhancement but hyperintense signal on DWI, it is not possible to differentiate between an infected focus and a small infarct. The differential diagnosis of multiple brain lesions in an immunocompromised patient includes lymphoma, metastatic disease, septic emboli, tuberculomas and multiple infarcts. It has been shown that aspergillosis characteristically involves the basal ganglia, indicating a

preference for lenticulostriate and thalamoperforator vessels, while corticomedullary involvement is typically less pronounced.[23] The apparent affinity of CNS aspergillosis for perforating artery distributions is most likely due to the invasive character of Aspergillus within the walls of the larger parent arteries subsequently compromising the origins of the perforating arteries. Pyogenic infection and thrombotic infarction generally do not involve the corpus callosum.[24] Temporal and frontal lobes are common sites for granulomas.[25]

Medical Management:

For a long time, the standard therapeutic regimen for cerebral aspergillosis following surgery remained intravenously administered amphotericin B combined with, or followed by, flucytosine or itraconazole.[2] Since the introduction of itraconazole, the first azole with significant activity against aspergillus, many clinical trials have proven its efficacy.[26,27] In addition to efficacy, other advantages of itraconazole therapy compared with amphotericin B are that it is less toxic and thus better tolerated although it shows variable and inconsistent absorption in some patients. Two newer parenteral antifungal medications (echinocandins) caspofungin and micafungin are also under scrutiny. However, all of the aforementioned medications are used mainly as adjuncts to surgical management, as despite improving outcomes compared to control groups, these show relatively poor penetration into the CNS. A newer triazole, voriconazole, is becoming increasingly popular. In several studies, and one large randomized trial conducted recently, voriconazole has proven to be more effective and less toxic than amphotericin B, and has since become the first line treatment of aspergillosis.[28] Recently, a very well conducted study based on an experimental murine model of CNS aspergillosis established within 5-week old male CD-1 mice has been published.[29] The investigators tested the relative efficacy of a number of anti-fungal medications, both as monotherapy, and in combination, using suboptimal as well as optimal-dose combination therapy. The study supported the potential of combination therapy as a mechanism to improve the outcome in CNS aspergillosis, showing that combination of sub-optimal doses of liposomal amphotericin B and voriconazole given concurrently was significantly efficacious in comparison with either monotherapy.

A few anecdotal reports have been published that describe treatment with intracavitary amphotericin B.[26,30] There may be some theoretical advantage in the administration of granulocye monocyte colony stimulating factors (GMCSF) to enhance neutrophil, monocyte and macrophage antifungal activity in vivo.[31] Recombinant γ-IFN can be given to improve the antifungal properties of polymorphonuclear cells and helper T cells by tilting their activities towards a Th1 response and inducing neutrophil-mediated fungal hyphal damage and also indirectly through tumor necrosis factor and macrophage inflammatory protein 1α.[31] However, these potential therapeutic strategies have not been tested clinically. It may be recalled here that almost all the literature on intracranial aspergillus infections in immunocompetent patients, describes the hosts as "apparently immunocompetent". It is possible that these "immunocompetent" patients may be suffering from sub-clinical qualitative, cellular or sub-cellular immune deficiency that is either unrecognized or as yet, poorly characterized. Such patients may benefit from these immuno-modulators and with the exception of high cost of these medications, there does not seem to be much harm in their routine administration to these patients.

Surgical Management:

There are no specific treatment recommendations for intracranial aspergillosis, as detailed data on patient survival is only available from case reports and case series.[26,27] However, despite newer, safer and more effective anti-fungal medications, the consensus is that the cornerstone of treatment remains surgical excision, a standard based largely on reports of personal experience; and more recently on the basis of a multifactorial risk analysis done by Schwartz et al on the data of a study population comprising mainly of immunocompromised patients on voriconazole therapy, which suggested improved outcomes in patients who had undergone neurosurgical intervention.[27] Besides, there are very few reports of patients surviving CNS aspergillosis on medical treatment alone. It cannot be over emphasized that surgical excision must always be followed by aggressive antifungal chemotherapy to achieve best response.[7]

As compared to radical surgical intervention, sub-radical excision aimed at establishing diagnosis and reducing disease burden followed by systemic antifungal therapy seems to be a better course of action.[3] This approach helps to minimize long-term neurological deficits that may arise as a result of radical excision, particularly in eloquent areas. However, when faced with a surgically removable lesion in a noneloquent area, the best plan would be to perform complete excision. Sub-radical resection may be reserved for lesions which are only partially resectable. Obviously, in a lesion occupying an eloquent area, where iatrogenic permanent neurological deficits seem inevitable even if sub-radical excision is attempted, a biopsy would suffice.

A similar approach is advisable in case of cerebral aspergillus abscesses. These should be excised completely if there is no risk of further neurological deficits as complete excision has been shown to improve outcome. Even lobectomy, in patients with a single aspergillus abscess is an acceptable surgical option when noneloquent areas of the brain are involved. On the other hand, when eloquent brain

areas are found to harbour an aspergillus abscess, aspiration may be the only surgical option which may be done more precisely under neuronavigation or stereotactic guidance, especially if the abscesses are deep-seated. This is not the optimal treatment option but may be considered as last resort as it is not curative, but may reduce disease burden. Instances where the nasal passages are suspected to be involved, there should be a thorough debridement of nasal passages, thereby depriving the fungus of a potential microaerophilic environment otherwise suitable for its proliferation.

Results and Complications:

Beside the general complications anticipated after major cranial surgeries, and the adverse effects described for the antifungal medications, some specific complications reported for these patients include massive anaphylaxis, meningitis, mycotic aneurysm formation, intracerebral haemorrhage, subarachnoid haemorrhage and hydrocephalus. Hydrocephalus is usually of communicating type, although non-communicating type may also occur. Perhaps the two most catastrophic complications, both unusual in etiology, are; widespread multifocal dissemination in the brain parenchyma/ ventricles and vascular infarcts involving major cerebral vessels, which may be remote from the site of surgery.[2]

Outcome of craniocerebral aspergillosis is different in

Table-1: Common clinical presentations.

Intracranial Disease
Headache
Sensory impairment
Cranial nerve deficits
Vomiting
Seizures
Hemiparesis
Altered consciousness
Paranasal Sinus Disease with Orbital Extension
Nasal stuffiness
Proptosis
Peri-orbital pain
Diplopia
Ophthalmoplegia
Visual deterioration
Chemosis

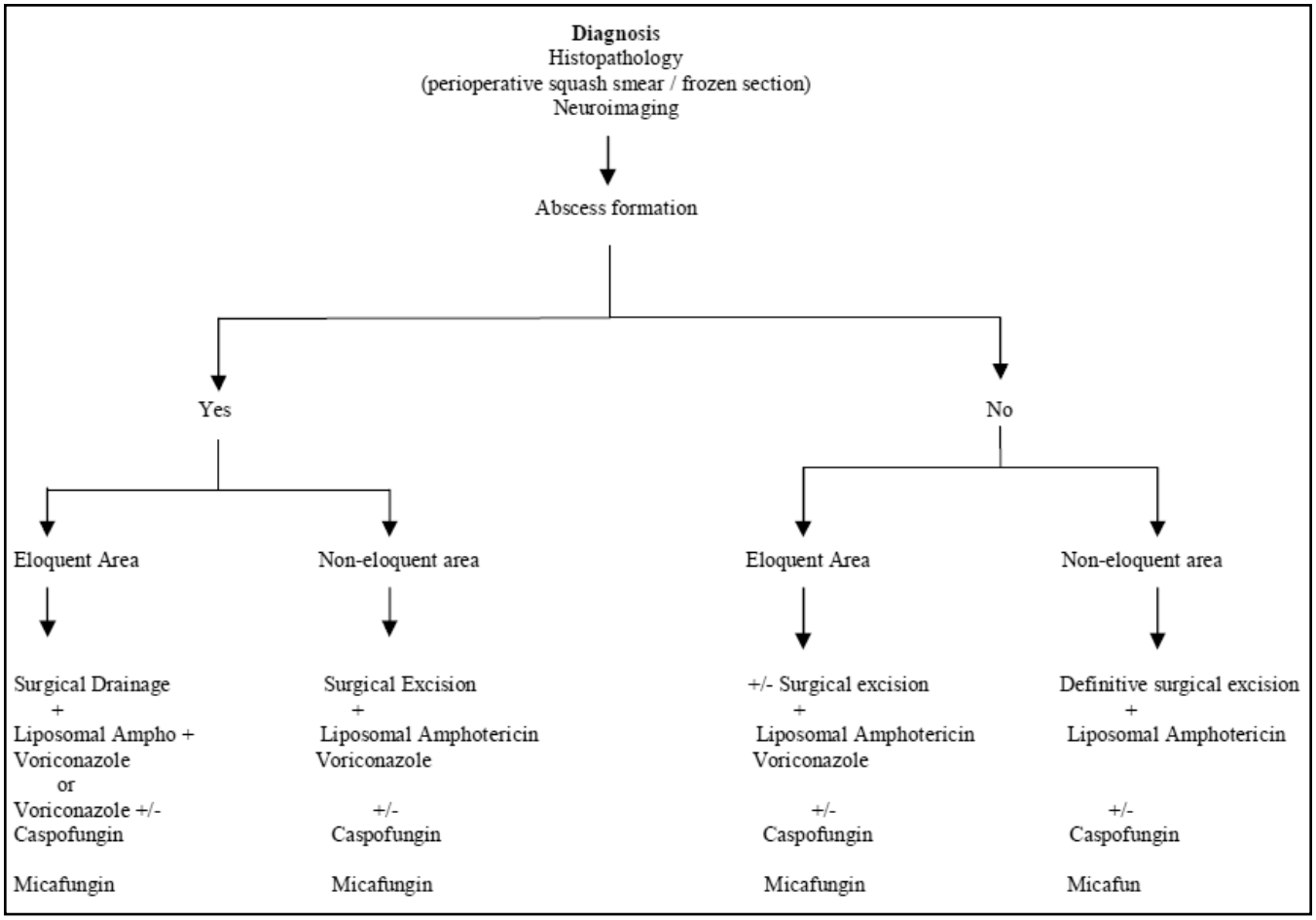

Figure: Algorithm for management of fungal lesions of the CNS.

Table-2: Neuroimaging features.

Radiological Findings
Abscess
Vascular infiltration
Infarction
Intra-axial space occupying lesion
Extra-axial space occupying lesion
Involvement of orbit with visible bone destruction
Involvement of sinuses with visible bone destruction (highly suggestive)
Commonly Involved Areas
Frontal
Temporal
Basal ganglia
Thalamus
Corpus callosum
Brainstem

immunosuppressed and apparently immunocompetent hosts.[32] In immunocompromised hosts mortality is reported to reach more than 95%, and even 100 % in patients with underlying malignancies.[33] In apparently immunocompetent hosts reported mortality varies from centre to centre, but ranges from 40 to 80%.[2] Patients harbouring mainly sinonasal disease with only orbital and/or cranial base bony invasion/destruction, carry a very good prognosis (mortality < 20%).[4] Outcome in extradural aspergillosis is much better than in patients with intracerebral involvement and outcome is worse in patients with intraparenchymal disease especially with vascular invasion.[2]

Our centre deals with a large volume of patients with isolated sinonasal aspergillosis, mainly catered by the otorhinolaryngologists.[34] As mentioned previously, these patients do extremely well with local clearance and antifungal medications, with the main concern being local recurrence. We also deal with a significant number of patients with intracranial disease, both extradural and intradural. Fortunately such patients are not so common.[2] Newer reports are strongly suggesting improved outcome with pre-medication prior to surgery have also emerged.[35]

Patients with extradural disease also do reasonably well with local debridement (whenever feasible) along with antifungal medications, the main risk being vascular invasion and dural breach, both of which greatly affect outcome. These patients are managed by the otorhinolaryngologists and neurosurgeons together, at times both operating at the same time. The most challenging group of patients remain the very few who harbour intracranial intradural disease. These patients are managed mainly by the neurosurgery team with assistance from otorhinolaryngologists. The input of ther specialties such as infectious disease experts, endocrinologists, microbiologists and intensivists is also of paramount importance.

Our institute is a tertiary care facility catering to an estimated population of 20 million. Over the past eight years, we have operated upon 17 patients with intracranial intradural aspergillosis. Of these 14 were males and 3 were females; the mean age of these patients was 37 ± 17 years (2-74 years) and the mean duration of symptoms was 3 ± 2 months (range 2 weeks to 6 months). All but three of these patients were immunocompetent, two patients suffering from haematological malignancies and one patient being a diabetic. The disease mainly involved temporal lobes in majority of patients (9 of 17). Pre-operative diagnosis of aspergillosis was suspected in 14 of these patients, based on clinical and radiological features, of which 13 received pre-operative antifungal medications. In five patients either the patient's condition or the extent of disease precluded radical resection and these patients underwent minimally invasive biopsies (3 patients), external ventriculostomy (one patient) or burr hole aspiration of abscess (one patient). All the rest of 12 patients underwent radical surgeries aimed at removing entire disease load. All patients were started on high dose antifungal medications post-operatively. At mean follow up of 5 months, all patients managed with minimally invasive biopsy and chemotherapy and half of patients managed with radical surgery along with chemotherapy expired. However, 6 of the 12 patients managed with radical surgery were still alive, all with good outcomes, four having a Glasgow Outcome Score (GOS) of 5 and two having a GOS of 4. Pre-operative neurological status was the single most significant indicator of poor outcome although none of the other factors such as age of patient, duration of symptoms, extent of disease or pre-operative administration of antifungal medications could be shown to affect the outcome, perhaps due to the small sample size.

Conclusion

Aspergillus infection of the CNS is an uncommon clinical entity, affecting mainly the immunocompromised. The disease presents in a number of unusual ways and although a multitude of clinical, biochemical and radiological features have been described, the diagnosis remains elusive. The problem is further compounded when the host is apparently immunocompetent, which lowers the clinical suspicion. Radical surgery followed by systemic antifungal medications offers the best hope for survival. Despite better understanding of the offending organism, pathophysiology, clinical course, and development of more effective antifungal medications, the prognosis remains poor. High index of suspicion, early diagnosis and aggressive surgical management, followed by medical therapy, by an inter-disciplinary team, may help to improve outcomes.

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