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Intracranial aspergillosis amongst immunocompetent patients: An experience with combined surgical and medical management of 18 patients

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ABSTRACT

Objective: Fungal infections of central nervous system (CNS) commonly affect immunocompromised patients, however, recently such cases have been reported even amongst immunocompetent patients.

Patients & methods: In this study, we retrospectively analyzed outcome of 18 immunocompetent patients with histopathologically proven intracranial Aspergillosis undergoing combined surgical and medical management.

Results: The age of patients ranged from 5-65 years. Fourteen out of 18 patients had well defined lesions while 4 had diffuse disease. Paranasal sinuses were involved in 8 & cavernous sinus in 3 patients. Six patients had hydrocephalus. Four patients developed infarcts during their clinical course. Surgical interventions included gross (n = 4) or subtotal excision (n = 8), decompressive craniectomy & biopsy of lesion (n = 4), biopsy only (n = 2) and ventriculoperitoneal shunt placement (n = 6). All patients received postoperative antifungal therapy. The duration of follow up ranged from 10-60 months. Overall mortality was 44.4%. Mortality amongst patients undergoing gross total and subtotal excision was 25% & 50% respectively. Patients undergoing DC had a mortality of 25%. Both patients undergoing only biopsy died. Hydrocephalus was associated with a very high mortality (83.3%). Amongst surviving patients (n = 10), 6 patients became disease free & rest 4 had stable disease at last follow up.

Conclusions: Intracranial aspergillosis is associated with high morbidity & mortality even amongst immunocompetent patients. An aggressive multidisciplinary management is thus needed to improve outcome. Our study shows that a combination of surgical excision or decompressive craniectomy and antifungal therapy can be helpful in improving prognosis of these patients.

1. Introduction

Fungal infection of central nervous system (CNS) is one of the most disabling and deadly diseases worldwide. Fortunately, the disease is relatively uncommon, accounting for less than five per cent of all CNS infections. [27]

Though fungi are ubiquitous in nature, distribution of fungal infections depends on the environment, climatic conditions, socioeconomic status, immune status, habits and genetic factors of the human hosts. [36] Yeasts, filamentous and dimorphic fungi are responsible for producing most of the infections in humans. Intracranial Aspergillosis (IA) accounts for 5–10% of all fungal infections involving the CNS [27,37]. IA is largely confined to immunocompromised patients, commonest risk factors being human immune deficiency syndrome, transplant recipients, neutropenia, hereditary immune defects, lymphoid malignancies, immunosuppressive medications, diabetes mellitus, intravenous drug abuse and mechanical breakdown of the blood brain barrier due to surgery or trauma [3].

Although IA commonly affects immunocompromised patients, recently cases of IA in patients with intact immune system have been reported [37] and this is a worrisome trend. The outcome in immunocompetent patients is, however, better as they respond better to conventional medical therapy and also better tolerate radical surgery in comparison to immunocompromised patients [37].

The available literature on IA is mostly focused on management of immunocompromised patients. The literature on management of IA amongst immunocompetent patients is, however, deficient and heterogenous, mainly consisting of case reports and few small series [4,5,14,16,17,20,27–,28,29,30,31,37,38,41], In this study, we retrospectively analyzed our experience with combined surgical and medical

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management of 18 immunocompetent patients with intracranial Aspergillosis over a period of five years. To the best of our knowledge, the present study is one of the largest series in available English literature, that has addressed the issue of combined surgical and medical management of invasive aspergillosis amongst immunocompetent patients. We feel that our experience in management of one of the deadliest infections to inflict CNS will help readers in management of such patients.

2. Materials and methods

Inclusiosn criteria:

1. Histopathologicvally proven cases of intracranial aspergillosis
2. Immunocompetent patients
3. Patients with available follow- up

Exclusion criteria:

1. Immunocompromised status
2. Follow-up not available

Immunocompromised states that were excluded included: HIV infection, diabetes mellitus, malignancy and patients on immunosuppressant drugs.

Eighteen immunocompetent patients with aspergillus infection of CNS undergoing surgical intervention between January 2013 to December 2017 in our department were included in the study. The study was conducted retrospectively and data was retrieved from inpatient and out-patient records, operative notes, and picture archiving and communication system (PACS). The duration of follow-up ranged from 10 months to 60 months.

All patients were investigated with plain radiography of chest, paranasal sinuses, contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) of brain, orbit and sinuses. A detailed cardiac evaluation including electrocardiogram (ECG), echocardiogram (ECHO), were performed. In addition to regular blood investigations including complete blood count, serological test for HIV was also carried out. Diabetes mellitus was excluded in all these patients.

The surgical strategies included excision of mass lesion, decompressive craniectomy in presence of diffuse disease with mass effect and ventriculoperitoneal shunt placement for associated hydrocephalus. All patients received antifungal therapy.

3. Results

3.1. Demographics

The age of patients ranged from 5 years to 65 years with a mean age of 27.83 years. 12 patients were male while 6 were female with male:female ratio of 2:1.

3.2. Clinical presentation

The duration of symptoms ranged from 2 days to 3 years. Commonest pattern of presentation was headache, vomiting with or without fever, altered sensorium, seizure and focal deficits (Table 1)

Out of 18 patients, 14 had well defined mass lesion. Commonest site of involvement was frontal region followed by temporal, parietal and occipital regions. In one case, there was involvement of petroclival region with extension into sellar suprasellar region and in another case fungal granuloma was found in cerebellopontine angle. Multiple lesions involving both anterior and posterior cranial fossae were seen in one patient. Paranasal sinus involvement was seen in 8 patients, cavernous sinus was involved in 3 patients and orbital involvement was seen in 2 patients. Four out of 18 patients had diffuse disease in the form of encephalitis, pachymeningitis and multiple microabscesses. Ventriculomegaly was seen in 6 patients. Four patients developed infarcts during the course of their treatment. Basilar artery thrombosis (n = 1), bilateral A2 ACA thrombosis (n = 1), internal carotid artery thrombosis (n = 1) and microvascular thrombi (n = 1) were responsible for infarcts in these patients (Table 2)

Table 1
Symptoms at presentation.

Symptoms	Number(%)
Headache	14 (77.8)
Vomiting	8 (44.4)
Seizure	7 (38.9)
Hemiparesis	7 (38.9)
Altered sensorium	6 (33.3)
Fever	5 (27.8)
Decreased vision	5 (27.8)
Proptosis	2 (11.1)
Cranial nerve palsy	2 (11.1)
Aphasia	2 (11.1)
Behavioral abnormality	2 (11.1)
Nasal discharge	1 (5.5)

Table 2
Clinical characteristics.

Parameter		Total
No. of patients		18
Mean age (5-65 yrs)		27.8
Gender	Male	12
	Female	6
Age group	Pediatric	4
	Adult	14
Type of lesion	Well defined	14
	Diffuse	4
Paranasal sinus involvement	Present	8
	Absent	10
Cavernous sinus involvement	Present	3
	Absent	15
Orbital involvement	Present	2
	Absent	16
Hydrocephalus	Present	6
	Absent	12
Infarcts	Present	4
	Absent	14

3.3. Radiological finding

Contrast enhanced MRI was done in all patients. Radiologically lesions appear isointense on T1 weighted images and very hypointense on T2 weighted images with either homogenous or heterogenous enhancement with perilesional edema with or without paranasal sinus involvement. Though a hypointense lesion is highly suggestive of a fungal lesion, tuberculoma also has similar imaging findings and is thus a close differential diagnosis. Meningioma is another close differential of a fungal lesion. In our country, preoperative misdiagnosis of tuberculoma is very common, as tubercular infection is quite prevalent in India.

Preoperative diagnosis of fungal infections was suspected based upon radiological findings in 5 patients. However, none of the patients received preoperative antifungal therapy based upon radiological findings. Preoperative antifungal therapy was started only in 3 patients who had undergone trans-nasal biopsy from paranasal sinuses. In all other cases, antifungal therapy was started post operatively, as it is our institutional policy to start antifungal treatment only when either there is a strong intraoperative suspicion of the lesion being fungal or there is definitive histopathological diagnosis. The reason for this practice is the similarity in radiological profile of fungal and tubercular lesions as well as the side effect profile of antifungal medications.

Table 3
Showing the effect of type of lesion, extent of excision and hydrocephalus on outcome.

Parameter				Total	Mortality
Type of lesion	Well defined	Excision	Gross total excision	4	1(25%)
			Sub total excision	8	4(50%)
		Decompressive Craniectomy with biopsy		1	0
		Biopsy only		1	1(100%)
	Diffuse	Decompressive Craniectomy with biopsy		3	1(33.3%)
		Biopsy only		1	1(100%)
Hydrocephalus	Present	With well defined lesion		4	3(75%)
		With diffuse disease		2	2(100%)
		Total		6	5(83.3%)
	Absent			12	3(25%)

3.4. Surgical management

Amongst the 14 patients with well-defined fungal granuloma, 12 underwent either gross total or subtotal excision. One of the patients had undergone fronto-temporo-parietal decompressive craniectomy with biopsy and another one had undergone only biopsy.

Five of these 12 patients undergoing excision died (mortality 41.66%). In this group of twelve patients, those having hydrocephalus had a higher mortality (75%, 3 out of 4 patients died). It is also to be noted that patient undergoing gross total excision had a mortality of 25% (1 out of 4 patients died) while in rest 8 cases where complete excision could not be achieved mortality was 50% (4 out of 8 died). One of the patients had well defined lesions in frontal region as well as posterior fossa. Frontal lesion was excised completely but the posterior fossa lesion was not excised as it was encasing the basilar artery. Postoperatively, the patient died of brainstem infarction due to basilar artery thrombosis while on medical management. One of the patients had involvement of sellar suprasellar area along with cavernous sinus and periocular region. This patient underwent biopsy only and died. The patient who underwent biopsy along with decompressive craniectomy survived (Tables 3 and 4).

Out of 4 patients with diffuse disease 3 had undergone decompressive craniectomy with 66.67% survival (2 out of 3 survived). The patient with diffuse disease who had undergone only biopsy died. Thus, both patients undergoing only biopsy, whether harboring diffuse disease or well-defined granuloma, died with 100% mortality. Ventriculoperitoneal shunts were placed in 6 patients with ventriculomegaly, two of them had diffuse disease. The mortality in patients with hydrocephalus was 83.33% (5 out of 6 died). Functional endoscopic sinus surgery was done in 2 of the 8 patients with sinus involvement and frontoethmoidectomy was done in one patient.

All patients had aspergillosis as the causative organism on histopathological examination. Biopsy of all cases showed fragments of dense fibrocollagenous tissue infiltrated by chronic inflammatory cells with random distribution of foreign body type and Langhan's type of giant cells. Special stains for fungi (PAS, GMS) showed typical septate, acute branching hyphae characteristic of aspergillosis.

3.5. Medical management

Twelve patients received a combination of Liposomal Amphotericin B and Voriconazole. Three patients received only voriconazole while only Amphotericin B was administered in 2 patients. In one patient post-operative antifungal could not be started as the patient died immediately postoperatively. The total dose of liposomal Amphotericin B administered was between 2.0–4.0 g m. In two patients, amphotericin B had to be stopped because of development of renal dysfunction or severe hypokalemia. Voriconazole was given for a duration ranging from 1 week (in patients who died at 1 week postoperatively) to 18 months.

The duration of follow-up ranged between 10–60 months. Overall mortality was 44.44%. The mortality in patients with definite excision of fungal granuloma was 41.66% with 100% mortality was seen in cases of biopsy only. However, patients undergoing decompressive craniectomy along with biopsy had an overall survival of 66.67%. In our study, the presence of infarct and hydrocephalus were associated with increased mortality (75% and 83.33% respectively).

3.6. Follow up (Table 4)

In our series, 8 patients died out of which 6 were hospital deaths and other two died at home after discharge from hospital. The rest 10 patients had complete follow up ranging from 10 to 60 months, the average follow-up being 25.4 months. In this study out of 4 patients who underwent gross total excision, 3 survived and out of 8 patients who underwent subtotal excision 4 survived. There was no recurrence of lesion in three patients who were discharged with antifungal therapy after gross total excision at last follow-ups of 48, 14 and 12 months

Table 4
Showing surgical intervention and outcome.

S. No	AGE	SEX	DIAGNOSIS	SURGICAL MANAGEMENT	OUTCOME	FOLLOW UP
1	18	M	Fronto temporo parietal fungal granuloma	STE	Discharged	Died at home 12 mo after Sx
2	25	F	Parieto-occipital fungal granuloma	STE	Discharged	Disease free at 60 mo f/u
3	40	F	Frontal & PNS fungal granuloma with HCP	GTE and VP shunt placement	Discharged	Disease free at 48 mo f/u
4	28	F	Basifrontal granuloma with b/l infarcts & HCP	STE and VP shunt placement	Died	Died on POD-7
5	65	M	Granuloma involving ACF/MCF and orbits	STE	Discharged	Stable disease at 31 mo f/u
6	34	F	Temporal granuloma with MCA/PCA infarct	STE	Died	Died on POD-7
7	15	M	Disseminated aspergillosis with multiple microabscesses	DC, meningeal biopsy, abscess aspiration	Discharged	Stable disease at 31 mo
8	15	M	Multiple microabscesses with HCP	DC with biopsy,VP shunt placement	Died	Died 4 mo after Sx
9	33	M	Fungal sinusitis, pachymeningitis & HCP	FESS and VP shunt placement	Discharged	Died at home 14 mo after Sx
10	35	M	Sphenopetroclival and sellar suprasellar mass	Biopsy	Died	Died on POD-6
11	28	M	Temporo-cavernous fungal granuloma	STE	Discharged	Disease free at 18 mo f/u
12	35	F	Anterior cranial fossa skull base granuloma	STE	Discharged	Stable disease at14 mo f/u
13	20	M	Temporal fungal granuloma with sinusitis	GTE	Discharged	Disease free at 14 mo f/u
14	19	M	Parietal fungal granuloma	GTE	Discharged	Disease free at 12 mo f/u
15	5	M	Frontal fungal granuloma with HCP	STE and VP shunt placement	Died	Died on POD-3
16	30	M	Temporo-cavernous and parietal fungal granuloma	DC and biopsy	Discharged	Disease free at 16 mo f/u
17	23	M	Fungal encephalitis with mass effect	DC and biopsy	Discharged	Stable disease at 10 mo f/u
18*	33	F	Basifrontal & posterior fossa granulomas with sinusitis & HCP	FESS, GTE and VP shunt placement	Died	Died 2 mo after Sx

PNS-paranasal sinuses; HCP-hydrocephalus; ACF/MCF-Anterior/middle cranial fossa; STE/GTE- Subtotal/gross total excision; DC-decompressive craniectomy; FESS-Functional endoscopic sinus surgery; VP-ventriculo-peritoneal; mo-months; Sx-surgery; f/u-follow-up; POD-postoperative day.

* Frontal lesion was excised completely but posterior fossa lesion was not excised.

(average follow-up: 24.7 months). One of these patients is disease free at 48 months. Two patients discharged with antifungal therapy after subtotal excision had complete resolution of lesion and remain disease free at a follow-up 60 and 14 months (average follow-up:37 months). The other two had static lesions without showing any sign of relapse at follow-ups of 31 and 14 months (average follow-up: 22.5 months). Three patients discharged after decompressive craniectomy and biopsy are doing well without recurrence with average follow-up of approximately 18 months.

4. Discussion

IA is an infrequent, opportunistic fungal infection of the central nervous system, accounting for 5–10% of all intracranial fungal pathology. [27,37] Aspergillosis is the commonest CNS fungal infection that causes intracranial granuloma formation.37] It mostly presents as intracranial space occupying lesion with commonest sites of involvement being frontal and temporal lobes. In our series, also aspergillus presented with well-defined mass lesion in 77.78% (14/18) cases, mostly involving frontal followed by temporal region.

The most common primary sites of aspergillosis are lungs, paranasal sinuses, and ear canal. [27,36,37] IA usually results from hematogenous dissemination from primary foci of infection in organs such as lungs, or from direct extension of infections from paranasal sinuses and calvarium, in patients with penetrating head trauma or following neurosurgical procedures. [37] Amongst the immunocompetent patients, contiguous spread from paranasal sinuses is more common. [35,37] Direct spread from one of the nasal sinuses causes intracranial growth mainly along the base of the skull and larger vessels. This generally leads to damage of cranial nerves I–VI. [42] In our series, cranial nerve involvement was present in two cases. IA can also produce single or multiple brain abscesses, epidural abscess, vasculitis, stroke-like illness, mycotic aneurysms, granulomatous mass and meningitis irrespective of immune status. [5] Marked vascular invasion with or without secondary thrombosis and with or without hemorrhage is the hallmark of IA attributed to its angio-invasive nature.36]

The literature for CNS fungal infection in immunocompetent host is sparse and has been mostly reported from India, Sudan, Pakistan, SaudiArabia, UAE, and a few other African most probably due to hot, dry climate, and low socioeconomic status in the above-mentioned regions. [2,23]

4.1. Clinical presentation

The typical clinical presentation of patients with IA is fever, headaches, nasal stuffiness, lethargy, proptosis, peri-orbital pain, mental status changes, or seizures with or without focal neurologic deficit like hemiplegia, cranial nerve palsy or vision changes. [21] In immunocompromised hosts sometimes an acute course characterized by rapid deterioration of the clinical picture usually ending with death may be observed. By contrast, a sub-acute or chronic form of meningitis was most frequent among immunocompetent patients [2]. Patients may also present acutely with cerebral infarctions or hemorrhage, a manifestation of vascular invasion by the fungus [32,33]. In our series infarcts were seen in 4 patients (22.2%). Mortality in patients with infarcts was 75% while the overall mortality was 44.44%.

The diagnosis of Aspergillus meningitis during life is challenging and accounts for only 55.9% of patients because the presenting symptoms are often non-specific, and diagnostic characteristics may be absent. [37] Due to aggressive and acute course of the disease in immunosuppressed hosts the chances of diagnosis are more in immunocompetent patients (69.2%) as opposed to immunocompromised individuals (39%) [2].

IA in immunocompetent patients produces a diagnostic dilemma as neither clinical nor the imaging features of CNS fungal infections are truly diagnostic of the disease and with patients being immunocompetent, the possibility of fungal infection is considered low on the list of differentials. [1] In our series also, in only 5 cases (27.7%) a preoperative diagnosis of fungal infection was considered.

4.2. Radiology of cerebral aspergillosis

The radiological appearance consists of iso- or hypo-intense lesions on T1-weighted MRI, which appear extremely hypointense on T2-weighted sequences and enhance brightly after administration of gadolinium. Such enhancement is usually limited to the rim, but homogeneous enhancement may also be present. [23]

Due to predilection of aspergillus for cerebral vessels multiple areas of infarction with or without associated hemorrhage may be present.

The characteristic CT finding of invasive aspergillosis of sino-nasal variety is presence of a hyperdense mass lesion in the sinuses along with bony expansion or erosion of sinus walls and/or cranial base is frequently observed. [37] Infarction with or without hemorrhage which are features of cerebral aspergillosis in case of vessel invasion are easily picked up by CT scan.

The differential diagnosis includes tuberculomas, meningioma, lymphoma, metastatic disease, septic emboli, and multiple infarcts. The diagnosis of aspergillosis is supported with the involvement of paranasal sinuses but it is not diagnostic on its own.

A lesion that is very hypointense on T2W images with associated perilesional edema and paranasal sinus involvement must be strongly suspected to be fungal and an aggressive approach towards treatment of such patients should be adopted (Fig. 1–3)).

4.3. Management strategies

The outcome of patients with IA without treatment is dismal. [11,37]. Antifungal medications, though a mainstay of management, alone seem to be inadequate as far as resolution of disease process is concerned. In literature, such success stories with medical management alone are limited to isolated case reports only. [6,12,29] The Infectious Diseases Society of America (IDSA) recommends combined surgical and medical management for IA [40]. The aim of surgery in IA is multifold. Surgical excision provides samples for diagnostic confirmation of pathology as well as for performing sensitivity testing. It also leads to debulking of disease load, thereby making treatment with antifungal medications more effective [34].

However, the mortality rate remains to be high (between 28% and 85.7%.) despite high doses of antifungal drugs and extensive surgery [5]. As immunocompetent patients respond better to treatment than those with impaired immunity, a more radical approach is recommended in patients with intact immune status [28].

4.4. Surgical management

There are no specific guidelines for IA as far as surgical intervention is concerned. Infectious Disease Society of America (IDSA) recommends that the extent of resection should be guided by the surgical accessibility of the lesions [40]. In literature, the type of surgical intervention opted by different authors is variable, with some authors performing only biopsy or aspiration of abscess while others completely excising the fungal lesion. [4,5,14,16,17,20,27–3137,38,41], Outcome of biopsy and aspiration only is unfavorable. The mortality after these minimally invasive procedures approaches 33%, relapse occurs in another one third. Only 32% of these patients survive and do well at follow up. [8,32]. In our study however, patients undergoing biopsy only had 100% mortality. Patients with relapse of fungal brain abscess after aspiration do poorly even if excision is done as the second operation. So, if the location of lesion is non-eloquent and surgically accessible, then excision should be considered over simple aspiration. [1,20,27], Delaying or avoiding this step of surgical excision also decreases the efficacy of concurrent medical therapy [23].

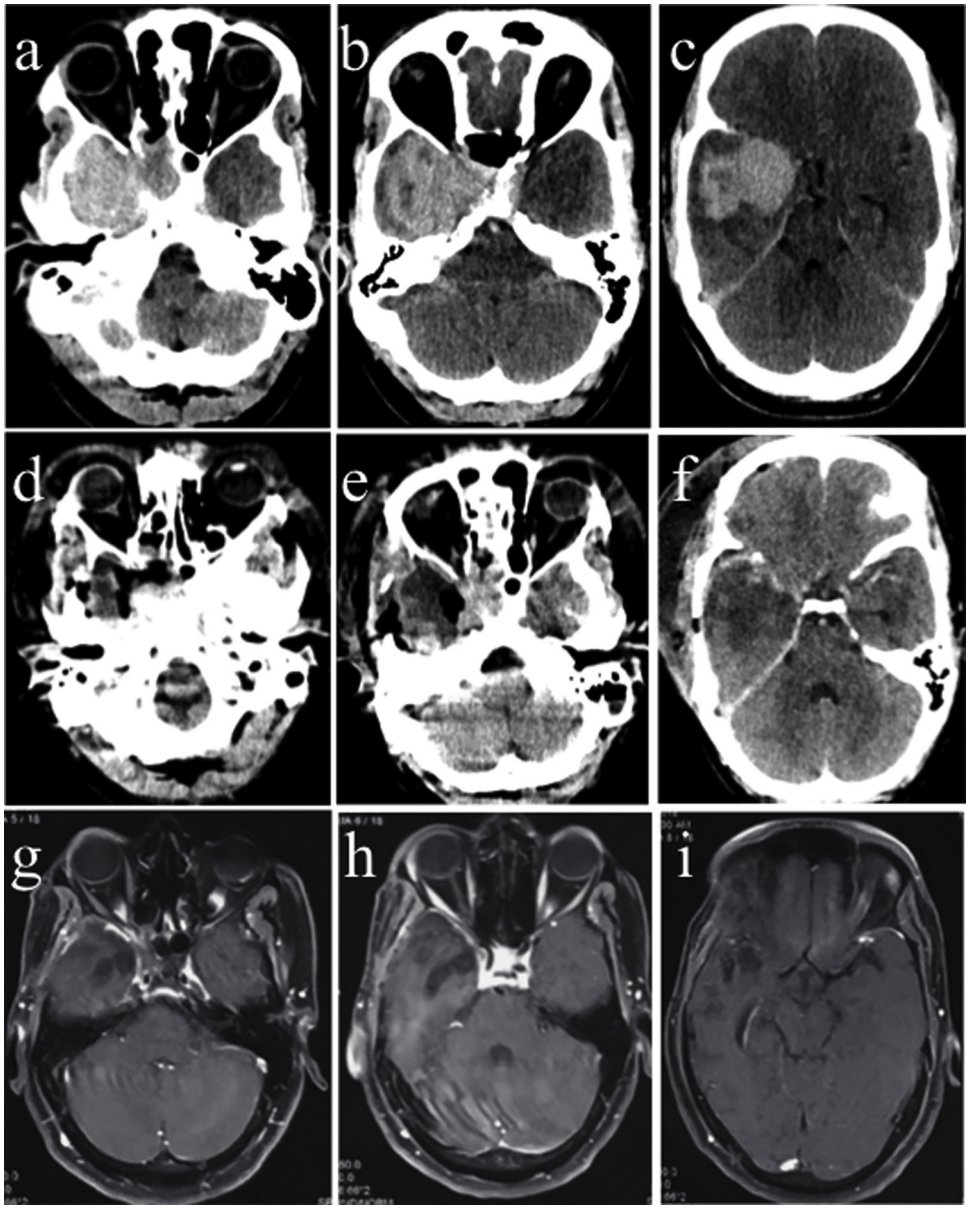

Fig. 1. A 28-year-old male patient (no:11 in Table 4) presented with headache and vomiting. Contrast CT scan revealed homogeneously enhancing lesion in right middle cranial fossa with involvement of cavernous sinus and extension into sphenoid sinus (a–c). Patient underwent craniotomy and subtotal excision of the lesion (d–f). Part of lesion involving cavernous sinus and sphenoid sinus was not removed (e). He received liposomal amphotericin and voriconazole. Follow up MRI at one year post surgery reveals complete resolution of the lesion (g–i).

Outcomes after surgical excision are generally favourable. Around 60% of immunocompetent patients with IA were reported to be well at follow-up after partial or complete surgical excision, [4,5,17,20,28,30,35,37,38] with rates of relapse of around 15% [1,5,28] and death in 25% of patients. [5,28,37]. In our series also 7 out of 12 patients (58.33%) with resectable lesions, who underwent total or subtotal excision, survived till last follow-up.

However, most of the series reported on surgical intervention in IA amongst immunocompetent patients have small number of patients and a thorough search of literature revealed only three series with more than 10 patients. [14,37,41]

Wasay et al [41] studied 25 patients with intracranial aspergillus abscess out of which 20 were immunocompetent patients. Their study, however, suffers from a serious lack of details about the type of surgical intervention, extent of excision of lesion, involvement of important neurovascular structures by the disease process, duration of medical therapy and details of follow-up.

In a study by Siddiquie et al [37] on aspergillosis amongst immunocompetent patients, 13 out of 25 patients had IA. The authors performed sub-radical excision aimed at establishing diagnosis and reducing disease burden, followed by systemic antifungal therapy. Overall mortality in their study was 54% with the longest follow up of 16 months. In our study overall mortality was 44.4% with an average follow-up of 25.4 months and longest follow-up of 60 months.

Schwartz et al.33 showed that the highly effective voriconazole therapy works well in patients who had undergone neurosurgical intervention. It can be said that medical and surgical management are complimentary to each other. Every surgical excision must always be followed by aggressive antifungal chemotherapy to achieve the best response [19,34,39]

Based on available literature it is difficult to say whether gross total or subtotal excision is better. [28,31,37] However, extensive excision is probably worthwhile in resource poor settings, as it may reduce the duration of medical therapy required and the cost involved [27,29].

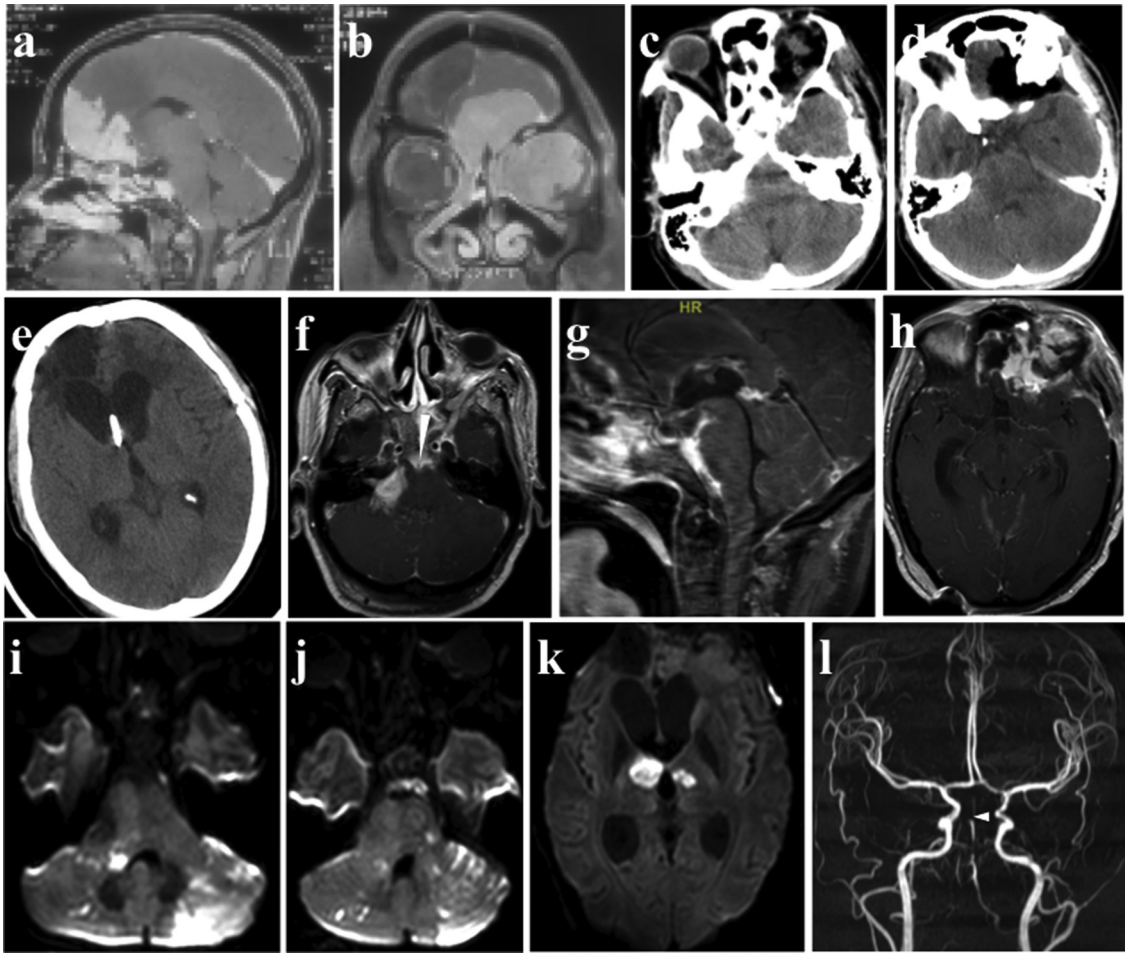

Fig. 2. A 33-year-old female patient (no:18 in Table 4) presented with proptosis, headache and vomiting. MRI revealed homogeneously enhancing lesion involving left basifrontal region, left orbit and paranasal sinuses (a&b). There was another lesion in prepontine region and right cerebellopontine angle (CPA) (a). Patient underwent gross total excision of basifrontal lesion (c&d) and also underwent ventriculoperitoneal shunt placement for hydrocephalus (e). However, two months after surgery, while on anti fungal treatment she deteriorated. MRI at this time showed persistent lesions in CPA and prepontine region (f–h) completely encasing and obliterating the basilar artery (white arrow head in f). Diffusion sequence revealed multiple infarcts involving bilateral cerebellar hemispheres, brainstem and thalami (i–k). MR angiography revealed basilar artery thrombosis (white arrow head in l).

Even lobectomy of non-eloquent areas can be considered in patients with a single aspergillus abscess. In the series reported by Nadkarni and Goel,26 four of seven patients with complete surgical excision survived (42.85% mortality). In our series patients with gross total excision had half the mortality (25%) than those patients where complete excision was not achievable (50% mortality).

However, Siddiquie et al [37] do not favor radical surgery due to risk of high morbidity associated with it. They prefer sub-radical excision aimed at establishing diagnosis and reducing disease burden, followed by systemic antifungal therapy. It minimizes the risks of permanent iatrogenic neurological deficit. However, radical excision can be attempted when the lesion is located in a noneloquent area as complete excision has been shown to improve outcome [26]. We completely agree to this approach as it is our practice to partially excise the lesion if it is involving important neurovascular structure. In our experience, even patients with incomplete excision had complete resolution of residual lesion on follow-up imaging and they did well clinically as well. The mortality rates in patients undergoing excision were much better (41.66%) than in those who underwent either biopsy or biopsy plus decompressive craniotomy (100%). Thus, maximum possible resection should be attempted, but not at the risk of causing vascular injury or neurological deficits.

When disease is diffuse, decompressive craniectomy helps in getting over the crisis of raised ICP, thereby buying time for antifungal drugs to control the disease activity.

The postoperative care in case of CNS fungal infection is very important. There may be sudden rise in the ICP due to “Forest Fire phenomenon” [23] which is characterized by rapidly increasing diffuse cerebral edema refractory to medical management often requiring decompressive craniectomy to prevent impending herniation. Postoperatively, patients with cerebral aspergillosis are at a greater risk of vascular complications, particularly in the setting of subtotal resection. Indeed, several cases of fatal and near-fatal cerebral artery infarction have been described, even remote from the site of infection. [13] In our series four patients developed infarction due to vascular thrombosis.

4.5. Medical management

Antifungal therapy for IA is complementary to surgical management. Amphotericin B has been the mainstay of aspergillosis therapy for the past quarter century. [19,28,37], However, serious side effects including infusion-related hypersensitivity reactions and acute kidney injury may cause discontinuation of therapy in upto 50% of patients [7,37], Liposomal Amphotericin B produce fewer adverse effects and long duration treatment is possible without need for discontinuation [23]. Combination therapy of a short course of intravenous amphotericin B followed by oral voriconazole or itraconazole is practiced by a number of institutions. [4,8,30],

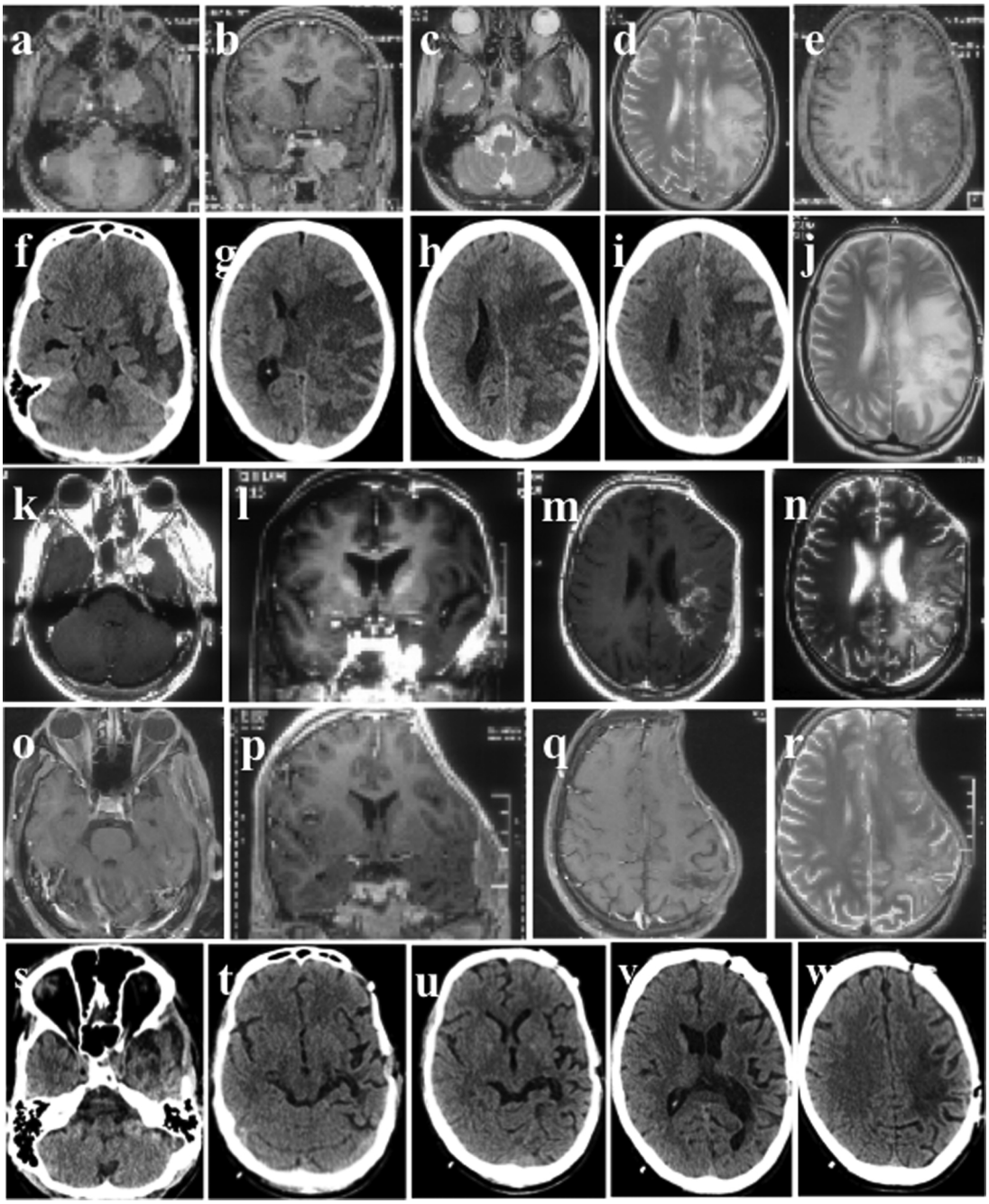

Fig. 3. A 30-year-old male patient (no:16 in Table 4) presented with altered sensorium and right hemiparesis. MRI revealed left medial temporal lesion with cavernous sinus involvement and left fronto-parietal lesions. Both lesions were hypo intense on T2W images and showed contrast enhancement (a-*J*). The fronto-parietal lesion was associated with significant peri-lesional edema and mass effect. The patient underwent decompressive craniectomy and biopsy from temporal lesion and received anti fungal therapy. Contrast MRI at 3 months shows reduction in size of temporal lesion and peri-lesional edema (k–n). MRI at one year shows complete resolution of both the lesions and peri-lesional edema (o–r). Patient underwent cranioplasty (s–w) and is symptom free at 16 months follow up.

At present voriconazole is recognized as a first choice agent for invasive aspergillosis by the IDSA and there are several reports supporting its efficacy over amphotericin B in cerebral aspergillosis with less toxicity and higher CSF penetration. [15,18,22,24,40] It is effective in cerebral aspergillosis irrespective of patient's immune status and may be given by the intravenous route immediately following surgery, followed by an oral course [25]. Side effects include hepatotoxicity and visual changes, including blurred vision and photophobia.

The choice of antifungal agent is largely influenced by institutional antifungal guidelines. In case of relapse sensitivity pattern may change and new sensitivity pattern should be established. [40]

Duration of medical therapy is controversial and highly variable in the literature. Most institutions employ between 6–18 months of antifungal therapy comprising of initial intravenous therapy, followed by oral treatment. [40] The duration of treatment depends upon the response of host to antifungal medication and residual size of lesion, which in turn depends upon location of lesion and general condition of the patient. In case of gross total resection, 6-month treatment course may have favorable outcomes [4,38]. However a minimum of 12–18 months of medical therapy should be considered for patients after subtotal excision [28,37]

In the present series, Amphotericin B was used alone in 2 patients. In 12 patients, a combination of Amphotericin B and voriconazole was used. The duration of anti-fungal therapy ranged from 1 week to 18

months.

4.6. Outcome

The immune status of host plays an important role in outcome of patients with IA. [9] In immunocompromised hosts mortality approaches 95% to 100%, worst outcome being in cases with underlying malignancy [10]. In apparently immunocompetent hosts reported mortality ranges from 40 to 80% [27,37]. The reason for better outcome in immunocompetent patients may be due to their better response to conventional medical therapy and greater tolerance to more radical surgery than patients with immunodeficiency. [37] This heterogeneity in clinical response necessitates consideration and development of management strategies specific to immunocompetent patients.

Our series, though small in number and retrospective in nature, does show the positive impact of surgical intervention on the outcome of immunocompetent patients with intracranial aspergilloma. Our study shows that excision is better than only biopsy (mortality 41.66 vs 100%). Further, gross total excision leads to better survival than subtotal excision (75% vs 50%). Our study also shows that decompressive craniectomy with biopsy improves survivability to 75% in patients with diffuse disease by tiding over the crisis of raised ICP till antifungal therapy takes care of the disease. We also found that hydrocephalus is a strong predictor of poor outcome (mortality 83.3%).

4.7. Limitations

The retrospective nature of study, and heterogenous patient population in terms of types of aspergillus lesions viz. localized and diffuse are some of the limitations of our study. The present study is one of the largest surgical series of IA amongst immunocompetent patients in available English literature. Despite some limitations, our study does shed some light on the possible beneficial effects of surgical intervention on IA.

5. Conclusion

Cerebral aspergillosis amongst immunocompetent patients is uncommon. Though it carries better prognosis as compared to immunocompromised patients, the prognosis is still dismal with high morbidity and mortality with medical therapy alone. Based upon our own experience and available literature, it can be concluded that surgical excision of well localized lesions seems to have a positive impact on disease control and outcome. Though the effect of extent of excision on outcome needs to be studied further, in our experience, complete excision is associated with better outcome than incomplete excision. Also, in patients with diffuse disease with raised intracranial pressure, decompressive craniectomy can be helpful in controlling the disease and might improve prognosis in these patients.

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Declaration of Competing Interest

The authors declare no potential conflict of interest

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