

## Intracranial Fungal Granuloma Various Treatment Modalities Depending Upon The Anatomical Structures Involved

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### **ABSTRACT:**

**Objective:** To determine the efficacy and achievement of better results by applying different modalities of management, depending upon the anatomical structures involvement.

**Material and Methods:** This is a vast study including 50 cases of intracranial fungal granuloma presenting in the department of Neurosurgery PGMI Lahore General Hospital, Lahore.

**Study duration:** The study duration was ten year from August 1998 to August 2008.

**Study Design:** Prospective and retrospective and observational.

**Results:** A total of 50 cases were included in the study. Sex incidence revealed male 30 (60%) and female 20 (40%) patients. The ratio of male to female was 3:2. The age range revealed youngest patient was 10 years of age and oldest patient was 58 years of age. Most of the patients (80%) were in the 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup> decade of life.

**Clinical presentation:** Most of the intracranial fungal granulomas were as a result of spread of fungal infection from paranasal sinuses. Out of total 50 cases 38 (78%) were secondary to paranasal sinus fungal infection only 10 cases purely intraparenchymal fungal granuloma with no evidence of nasal sinus involvement. In 2 (4%) cases fungal osteomyelitis was seen following surgery for removal of extradural haematoma. Other clinical symptoms were headache in all cases. Features of sinusitis (allergic or chronic) in 35 (70%) Vomiting 45 (90%) Nausea 45 (90%), proptosis 30 (60%), deterioration of vision 28 (56%) seizures 20 (40%) in cases. Frontal lobe syndrome in 25 (50%) cases. Drowsiness 10 (20%) cases and involvement of cranial nerves in 30 (60%) cases. Papilloedema was seen in 28 (50%) cases. Associated diseases like Diabetese mellitus was present in 25 (50% cases). Hypertension in 15 (30%), chronic live disease in 5 (10%) cases and compromised kidney in 5 (10%) cases.

**Treatment:** Treatment was offered according to the anatomical structures involved and patients were divided in 4 groups. **Group A:** skull base extradural fungal granuloma secondary to its spread from paranasal sinuses. These 17 cases, were treated by transthemoidal approach (7 cases) combined approaches involving maxillotomy with transcranial approaches (05 cases) and only endonasal clearance of the disease (05 cases).

**Group B:** Extracranial fungal granuloma with spread upto the brain parenchyma: In this group 21 cases were included, surgical procedures performed were transthemoidal approach in 3 cases, Bur hole Biopsy in 7 cases, craniotomy and excision 05 cases and only endonasal clearance in 6 cases. This group revealed excellent result in 1 case treated with a new drug variconazole, other cases revealed, good results in 2, fair in 14 cases and mortality in 4 cases. This represents the fulminant form of the disease where both extradural and intradural skull base disease was prevailing.

**Group C:** This group involves the **purely intraparenchymal disease** with no evidence of Nasal sinuses involvement. This group included 10 cases. The treatment offered was Burhole Biopsy 2 cases, craniotomy and removal of fungal granuloma in 8 cases. The results were excellent 3 in cases, good in 2 cases (both died later on). Fair in 1 case (died later on) and immediate mortality was seen in 4 cases within 3 weeks and delayed mortality was seen in 3 cases (2 months to 2 years)

**Group D:** Post-traumatic fungal granuloma. In this group 2 cases were included, operated for extradural haematoma. Later on they suffered from fungal granuloma and wound infection. Both cases were operated for removal of bone flap and antifungal therapy was given Both revealed excellent results.

**Overall Results:** Excellent result in 12 (24%), Good in 14 (28%), Fair in 6 (12%) cases. Mortality was 18 (34%) cases.

**Conclusion:** It is concluded from the study that when there is intradural extension of the disease then only Bur hole Biopsy should be performed if necessary, otherwise antifungal treatment can be given on clinical basis as well. Attempt to excise the lesion can flare up the disease process, hence should not attempted. If one has performed craniotomy for excision of tumor but per operatively surgeons had the impression of fungal granuloma, fungal stain should be sent immediately to confirm the diagnosis and antifungal should be started immediately. These patients had the tendency to deteriorate on 4<sup>th</sup> – 6<sup>th</sup> day post operatively, such patient should be subjected for selective hyper-ventilation for one week to 10 days or till the clinical condition of the patient improves significantly. The new magic drug voriconazole should be utilized, although yet it is very expensive drug and its availability is also limited. Associated conditions like diabetes mellitus, metabolic deficiencies should be managed properly for better results.

**Keywords:** Fungal granuloma brain, Fungal infection brain, Nasal fungal granuloma, surgical approaches for anterior skull base, maxillotomy.

**Abbreviation:** PNS = Paranasal sinus.

## INTRODUCTION

Intracranial fungal infection of central nervous system is a relatively uncommon infection mainly among immunocompromized patients. It manifest as meningitis, infraction, mycotic aneurysm or (SOL).<sup>1</sup> Intracranial fungal granuloma are rare, mostly they are due to contiguous spread of infection from paranasal sinuses and rarely may be due to hematogenous spread from focus in lung.<sup>2,3</sup> Isolated cerebral fungal granuloma are extremely rare without obvious extracranial focus of infection.<sup>4</sup> Diabetes mellitus is a frequent predisposing illness in patients with cerebral fungal masses especially with paranasal sinus involvement likewise HIV infection, organ transplantation. Cancer chemotherapy, prolonged steroids use, autoimmune disorder all are predisposing factors for intracranial fungal infections.<sup>5-7</sup> Among immunocompetent patients intracranial fungal infections more commonly found in Pakistan, India, Saudi Arabia, Africa and California in United States.<sup>8,9</sup> The hot dry climate with high content of aspergillus spores in atmosphere due to agriculture dust may be the culprit for infections among patients residing in these regions. Very rarely fungal infections may follow direct inoculation of brain following trauma and surgery.<sup>10</sup> Aspergillus spp is the most common causative agent for central nervous system fungal infections, Aspergillus flavus in immunocompetent while Aspergillus fumigates among immunocompromized patients. Cryptococcus, mucormycosis, candida and cladosporium can also cause

cerebral fungal infections.<sup>5,11</sup> Contrast enhanced C.T. and MRI of brain are investigations of choice. Neither of these provide definitive diagnosis, they only detect intracranial mass or masses and involvement of paranasal sinuses.<sup>12-14</sup> On MR spectroscopy determination of lactate and NAA peaks and choline creatinine ratio differentiate between infection and mitotic lesions.<sup>15</sup> The definitive diagnosis is established by tissue biopsy. Fungal hyphae are poorly visible on routine hematoxylin eosin stain and are better demonstrated on periodic acid Schiff and Gomorimethanamine silver stain.<sup>16</sup> Treatment of fungal infections of central nervous system include both surgical removal of mass lesions and adequate course of antibiotic therapy. Antibiotic for fungal infections are Amphotericin B, Flucytosine and Certain imidazole compounds.<sup>17,18</sup> In spite of several advances in imaging and surgical techniques and even the advent of some newer antifungal drugs the prognosis of intracranial fungal infection is not so hopeful.<sup>18,24,25</sup>

Intracranial fungal infection has high mortality and morbidity and is a big challenge for the neurosurgeons to treat these cases. No single approach or modality of treatment can be applied for all these cases. The surgical approach if mandatory has to catered depending upon the anatomical structure involved.

A new drug voriconazole is effective for the treatment f fungal brain infection. It is 8 times more effective and less serum level is required for therapeutic

results. Its side effect are also less as other drugs have Nephrotoxic effects with prolonged uses.

## RESULTS

### Sex Incidence

Sex incidence revealed male 30 (60%) and female 20 (40%) patients. The ratio of male to female was 3:2.

### Age Incidence

The age range revealed youngest patient was 10 years of age and oldest patient was 58 years of age. Most of the patients (80%) were in the 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup> decade of life (as shown in Table 1).

**Table 1: Age Incidence.**

Age	No.	Percentage
00 – 10	01	02%
11 – 20	04	08%
21 – 30	05	10%
31 – 40	10	20%
41 – 50	20	40%
50 – 60	10	20%
More than 60	Nil	-
Grand total	50	100%

### Clinical Features

Most of the intracranial fungal granulomas were as a result of spread of fungal infection from paranasal sinuses. Out of total 50 cases 38 (78%) were secondary to paranasal sinus fungal infection only 10 cases purely intraparenchymal fungal granuloma with no evidence of nasal sinus involvement. In 2 (4%) cases fungal osteomyelitis was seen following surgery for removal of extradural haematoma. Other clinical symptoms were headache in all cases. Features of sinusitis (allergic or chronic) in 35 (70%) Vomiting 45 (90%) Nausea 45 (90%), proptosis 30 (60%), deterioration of vision 28 (56%) seizures 20 (40%) in cases. Frontal lobe syndrome in 25 (50%) cases. Drowsiness 10 (20%) cases and involvement of cranial nerves in 30 (60%) cases. Papilloedema was seen in 28 (50%) cases. Associated diseases like Diabetese mellitus was

present in 25 (50% cases). Hypertension in 15 (30%), chronic live disease in 5 (10%) cases and compromised kidney in 5 (10%) cases.

Depending upon the anatomical structures involved, cases were divided into 4 groups (A to D) as below:

### Group A: Skull Base Extradural Fungal granuloma.

In this group there was primary involvement of paranasal sinuses due to allergic Rhinitis or chronic sinusitis leading to fungal granuloma which had extended to the skull base but yet extra dural lesion only. A total of 17 cases were included in this group.

### Sex Incidence (Group A)

Ten (50%) were male and 7 (41%) were female.

### Age Range (Group A)

Youngest patient was 10 years of age and oldest patient was 58 years of age. Most of the patients were in the 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> decades. Table 2 shows the age range according to the decades.

### Clinical Features of Group A

All cases had involvement of paranasal sinuses due to allergic rhinitis or chronic sinusitis with superadded fungal infection which spreaded towards the skull base. The important features were proptosis 15 (88%) cases, Nasal Blockage 15 (88%) cases, headache all cases, vomiting 16 (94%) cases, deterioration of vision 12 (71%) cases, seizures 5 (29%) cases. Loss of smell 14 (82%) cases. H/o fever 10 (59%) cases. Papilloedema was seen 5 (29%) cases.

**Table 2: Group A – Age Range.**

Decade	No.	Percentage
1 <sup>st</sup>	1	6%
2 <sup>nd</sup>	1	6%
3 <sup>rd</sup>	4	24%
4 <sup>th</sup>	5	29%
5 <sup>th</sup>	5	29%
6 <sup>th</sup>	1	6%
Total	17	100%

**Table 3:** Group A Site Involved, Operative Procedure Complications and Results.

Sub-group	Site Involved	Cases	Operation	Cases	Complication	Treatment	Outcome
A 07 cases	Paranasal sinus, Medial orbital angle Sphenoid sinus Anterior skull base	7 4 2 7	Transethmoidal approach	7	Nil	Diflucan 3 cases Sporonox 4 cases	Excellent – 2 Good – 5
B 05 cases	Maxillary sinus Ethmoidal sinuses Retroorbital Nostril Frontal Sinus	5 3 2 3 3	Maxillotomy with combination of Frontal craniotomy Bifrontal craniotomy Lateral orbitotomy Endonasal clearance of Fungal granuloma	1 2 1 1	Recurrence of Endonasal fungal granuloma in 1 case	Injection Amphotericin B 2 weeks followed by oral therapy with DIFLU- CAN 3 cases Sporonox 2 cases for 1½ year	Excellent – 1 Good – 3 Fair – 1
C 05 cases	PNS involved Ethmoidal Sphenoidal Anterior Skull base	5 1 5	Only Endonasal clearance of Fungal mass. Extradural mass managed conservatively	5	Nil	Injection Amphotericin B for 1 – 2 weeks followed by oral anti fungal Sporonox – 3 cases Diflucan 2 cases for 1 year	Excellent – 3 Good – 2
Total 17 cases							

**Investigations**

X-ray PNS revealed involvement of paranasal sinuses in 17 cases.

Plain and contrast C T Scan brain was performed in all 17 cases while special protocol for paranasal sinus was performed in 6 cases only. MRI brain was performed in 13 (76%) cases.

**Site:** CT Scan brain (PNS) and MRI revealed site of fungal granuloma as shown below in table 3. This table also shows the management offered to these cases.

**Group B Extradural fungal granuloma with spread upto the brain.**

In this group, maximum number of patients were seen, 21 (42%) suffered PNS involvement leading to the fungal granuloma formation. The fungal granuloma then spread to the skull base gradually invading the dura matter and finally spreaded to the brain.

This variety indicate most fungal granuloma. Its management was further subdivided into 4 groups

depending upon the spread of the fungal granuloma. The management and results are shown in the table 4.

**Important Observation in Group B**

1. In this group one young patient of 35 years with extensive spread of fungal granuloma from paranasal sinuses to the frontal and temporal lobes was managed with injection **voriconazole** followed by oral capsule of **VARICONAZOLE** for 6 months. This patient revealed excellent recovery and intracranial lesion resolved completely within 3 months of treatment variconazole. This is our small experience of one case, voriconazole is a good drug to treat the fungal granuloma brain but is very expensive and availability is also limited.
2. Once fungal granuloma originating from PNS had involved the dura matter and involved the brain parenchyma, these cases of brain fungal infection should not be operated for excisional Surgery. Inthese cases surgery will flare up the disease process.

**Table 4:** Group B: Extradural Fungal Infection Spreaded upto the Brain Management and Results

Sub-group	Site	Cases	Operative Procedure	Complications	Treatment	Outcome
Transthmoidal approach 03 cases	PNS, Skull base Frontal lobe	3	Transthmoidal approach for biopsy	Fulminant course 1 and died	Injection Amphotericin B and oral Sporonox	Mortality = 1 Fair = 2
Burhole Biopsy 07 cases	PNS, Skull base Frontal lobe	7	Burhole Biopsy	Rapid duration on 5 <sup>th</sup> day in 5 cases and died	Injection Amphotericin B	Good = 1 Fair = 1 Mortality = 5
Craniotomy and Excision 05 cases	PNS all Temporal lobe Frontal lobe	4 3 2	Craniotomy	All deteriorated on 5 <sup>th</sup> – 7 <sup>th</sup> post operative day in 4 cases	Injection Amphotericin B	Fair = 1 Mortality = 4
Conservative treatment 06 cases	PNS all cases Frontal lobe Temporal lobe Multiple sites	6 3 3 1	All managed conservatively except nasal clearance of fungal infection in 6 cases	Progressively Fulminant deterioration in 3 cases and death	Voriconazole injection 2 weeks & oral – 8 months in 1 case. All other Amphotericin B – 4 weeks & oral therapy upto 2 years	Excellent = 1 case Good = 1 Fair = 1 Mortality = 3 cases

**Table 5:** Group C: Management and Results.

Case		Surgical Procedure	Immediate Outcome	Follow up 2 months	Four month	One year	Two years	Four years
1	Sex, age Female 35 years	Bur hole Biopsy	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
2	Male 55 yrs	Bur hole biopsy	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
3	Male 18 yrs	Craniotomy twice	Good	Good	Good	Good	Died	
4	Male 35 yrs	Temporal Craniotomy	Died					
5	Male 25yrs	“	Died					
6	Male 30 yrs	“	Died					
7	Male 55 yrs	“	Died					
8	Male 52 yrs	Craniotomy twice	Good	Died				
9	Female 55 yrs	Craniotomy	Excellent	Excellent	Excellent	Excellent	Excellent	
10	Male 55 yrs	Craniotomy	Fair	Fair	Died			

3. Patients suffering from diabetes mellitus and other systemic diseases have poor body defence system, hence brain fungal infection spreads more rapidly and had poor prognosis. These cases can be considered for improving the body immune response by transfusing interferon or amino acid etc and improving the dietary status of the patient, we had good response with these supportive therapy in 1 patient.

## GROUP C:

### Intra-parenchymal Group

A total of 10 cases with purely intra parenchymal fungal granuloma were operated. Eight were males only 2 were female with male to female ratio of 4 to 1. Before surgery, there was clue of fungal infection in 2 cases due to MRI picture of perilesional edema. Only Bur hole biopsy was performed to confirm the Histopathology. Both these cases showed excellent results with oral anti fungal SPORONOX 1 case and DIFLUCAN (1 case each). First case presented with headache, vomiting, Nausea, deterioration of vision. Histopathology was Aspergillosis. She recovered with SPORONOX 500 mg three times a day for 2 years when parasellar and intra-parenchymal lesion vanished completely within 2 years.

Second case also presented with Headache vomiting, nausea, deterioration of vision. He was male of 55 years and suffering from diabetes mellitus and Hepatitis C (HCV positive). CT Scan and MRI revealed lesion in the occipital region with adjacent brain edema. He was also operated by simple Bur hole and tissue was sent for histopathology (HP) which revealed fungal granuloma. That case also revealed excellent result. He used capsule DIFLUCAN (Fluconazole) for about 1 year.

In this group out of remaining 8 cases two cases were operated twice. Both cases had one lesion in temporoparietal region and another lesion in left parietal region. 1st Case was male 17 years of age presented with headache vomiting deterioration of visions and left hemiparesis, CT Scan brain revealed almost uniformly enhancing lesion temporoparietal region. He was operated upon, craniotomy and Near total excision of lesion was performed. The histopathology was tuberculoma in this case. He recovered well and got ATT for 12 months. He remained well for 8 months, then there was recurrence of symptoms and signs. CT Scan brain showed contrast enhancing lesion in the opposite parietal lobe (left side). He was again operated by

craniotomy and removal of lesion from left parietal region. This time the histopathology was fungal granuloma. He was treated by Amphotericin B, for 2 weeks then oral Cap DIFLUCAN for 1 year. He improved initially but he deteriorated rapidly, steroids were started he deteriorated further, steroid were stopped. He again recovered with anti fungal treatment gradually. Finally he expired after 3 year with a 4<sup>th</sup> episode of rapid deterioration of conscious level. The second case who was operated twice had a tumor like lesion (R) parietal region. He was operated by craniotomy and complete removal of lesion was performed. The histopathology was not exactly conclusive as it showed picture of astrocytoma III as well as fungal hyphae. He was also suffering from diabetes mellitus. He recovered gradually. Ventilator was used for 1 week post operatively, after fist surgery.

Considering the course of disease we treated with anti fungal treatment (Injection Amphotericin B was given). He improved gradually. In the follow-up CT Scan brain, the lesion on opposite site was progressively increasing while there was no recurrence on operated side (right side). As the previous histopathology was not exactly conclusive hence he was operated again for removal of parietal region. This time, the histopathology was very clearly fungal granuloma. Initially he improved but after 1 week he deteriorated rapidly and died within next 1 week. Among remaining 6 cases, all had features of raised intracranial pressure and were also suffering from diabetes mellitus. CT Scan brain / MRI of all cases revealed supratentorial enhancing lesion just like meningioma in 4 cases. All were operated by temporal craniotomy with suspicion of meningioma preoperatively, all cases were looking like meningioma but all had fungal granuloma in histopathology. All four cases died within 2 – 3 weeks.

Two final cases in this group who survived post operatively. One female 45 years of age had features of raised intra cranial pressure and she was drowsy. CT Scan brain revealed 2 lesions, one enhancing lesion was in the temporal lobe while other lesion was in the parietal lobe, with peripheral enhancement, lesion was just like glioma. Both lesions were removed totally in the same sitting by performing big craniotomy flap exposing temporal and parietal lobes. This female patient was put on elective hyperventilation for 5 days post operatively. She recovered well, she was also given interferon therapy for 1 week to increase the body resistance. She recovered well but deteriorated, 2 months post operatively. Again she was managed con-

**Table 6: Overall Outcome in Relation to Group and Treatment.**

Group A / Subgroup	Surgical Approaches	No.	Medical Therapy	Outcome
Group A Skull base Extradural fungal Granuloma Sub group: Transethmoidal Approach 07 cases	Transethmoidal approach	7	Injection Amphotericin B 1 – 2 weeks then oral drugs like DIFLUCAN (03) and SPORONOX 4 cases	Excellent 2 Good = 5
Group A Sub Group II Maxillotomy and Combined approaches 05 cases	Maxillotomy With combined approach like Frontal craniotomy Bifrontal craniotomy Endo Nasal Clearance	2 2 1	Injection Amphotericin B 1 – 2 weeks then oral drugs like DIFLUCAN and SPORONOX	Excellent – 3 cases Good = 2 cases
Group A Sub Group III Conservative 05 cases	Only endonasal clearance of fungal mass No surgery for extradural mass	5	Injection Amphotericin B 1 – 2 weeks then oral drugs like DIFLUCAN and SPORONOX	Excellent 3 cases Good 2 cases
Group B Extradural fungal granuloma spreaded upto the brain – 21 cases	Transethmoidal Bur hole biopsy Craniotomy & excision Endonasal clearance only	3 7 5 6	Voriconazole 1 case. All other cases by Injection Amphotericin B and oral anti fungal	Fair 2, Mortality 1 Good 1, Fair 1, Mortality 5 Fair 1, Mortality 4 Excellent 1, Good 1, Mortality 4
Group C Intra parenchymal Fungal granuloma 10 cases	Bur hole biopsy Craniotomy (2 cases operated twice)	2 8	Amphotericin B for 2 – 3 weeks followed by oral therapy (Sporonox & Diflucan)	Excellent 3 Good 2 Fair 1 Mortality 4
Group D Post traumatic fungal Osteomyeletes	Removal of Injected Bone flap	02	Injection Amphotericin B 1 – 2 weeks followed by oral therapy Sporonox for 3 – 6 months	Excellent 02
<b>Over all outcome</b>				Grand Total Excellent 12 (24%) Good 14 (28%) Fair 6 (12%) Mortality 18 (36%)

servatively. Finally she recovered well, results labelled good in this patient.

The tenth case of this group had features of raised intracranial pressure. CT Scan brain revealed left parietal enhancing lesion with suspicion of brain tumour.

He was operated by craniotomy and removal of tumor. The histopathology was aspergillosis. He recovered well with by Injection Amphotericin B and then oral treatment. He was discharged in good condition. After 2 months he again deteriorated rapidly and was

admitted in serious condition. His CT Scan brain revealed gross Hydrocephalus but no residual fungal lesion. He expired rapidly before performing any procedure for acute Hydrocephalus. Thus out of 10 cases 2 cases survived in whom only diagnostic Bur hole was performed to confirm the nature of lesion and one lady with 2 adjacent lesion in temporal and parietal region, both removed completely and she was hyper ventilated for 1 week electively also survived.

Other 2 cases survived initially but both died after 2<sup>nd</sup> surgery for removed of second lesion in opposite hemisphere 6 weeks and 2 years after 1st surgery. Another case survived immediately post operatively but died of acute hydrocephalus after 3 months of first surgery.

Four cases operated by supratentorial craniotomy could not survive. All of them deteriorated after 4 – 5 days progressively and all 4 died within 3 weeks inspite of antifungal treatment.

#### **The important observations in Group C:**

1. Most of these patients deteriorates on the 5<sup>th</sup> day post operatively hence post operative elective hyperventilation is required.
2. Bur hole diagnostic biopsy should be performed wherever there is doubt of fungal infection.
3. Steroids should not be used in fungal infection.

#### **Group D Post Traumatic Fungal Wound Infection and its Spread**

In this we included 2 cases both were child 12 and 13 years respectively. Both were operated for removal of extradural haematoma by craniotomy flap. In both cases wound got infected 2 weeks post operatively which did not settled in spite of multiple and prolonged antibiotic use. Then biopsy of effected tissue was taken which revealed **Aspergillosis** fungal infection in one case and **candida** fungal infection in second case. Initially in both cases oral antifungal SPORONOX was used but wound did not settled. Skull X-Ray revealed osteomyelitis in both cases.

Hence in both cases infected bone flap and fungal tissue was removed. In second case fungal infection was extending to the brain through the involved dura matter hence near total fungal granuloma was removed in second case. Both cases revealed excellent results and settled with SPORONOX used for 3 – 6 months.

#### **Overall Outcome**

The overall outcome of all 50 cases is shown in Table

6. Excellent result in 12 (24%), Good in 14 (28%), Fair in 6 (12%) cases. Mortality was 18 (34%) cases. The important observations are as below:

#### **The important observations**

1. Most of these patients deteriorates on the 5<sup>th</sup> day post operatively hence post operative elective hyperventilation is required.
2. Bur hole diagnosis biopsy should be performed wherever there is doubt of fungal infection.
3. Steroids should not be used in fungal infection.

#### **DISCUSSION**

Intracranial fungal infection is an uncommon infection but now trend has been changed. Fungal brain infection is being increasingly diagnosed, not only in immunocompromized but also in immunocompetent patients especially in subcontinent. Environmental pollution causes allergic rhinitis and the nasal blockage if not treated properly leads to super added fungal infections in paranasal sinus which can extend to base of skull extradurally and later on to brain parenchyma.<sup>19,20</sup>

The high rate of mortality and morbidity associated with fungal granuloma brain is a challenge for neurosurgeons. The high incidence of allergic Rhinitis due to environmental pollution, allergins leads to the nasal blockage which if not treated properly leads to the superadded fungal infection in the paranasal sinuses which can spread to the skull base extradurally initially and if untreated, can of spread to the brain parenchyma. Once it involves the brain parenchyma then the course of disease is usually fulminant. Most of the antifungal drugs cannot eliminate the fungal granuloma as equally as anti tuberculous drugs can resolve the brain tuberculoma very effectively. However a new drug voriconazole is very effective for the treatment of fungal granuloma<sup>24</sup> but it is very costly and its availability is also limited in Pakistan.

Our study is one of the biggest study in Pakistan including 50 cases of fungal granuloma during the last 10 years. Dubey and Patwardhan represented a large series of 40 patients over 22 years from 2 centers of India and United States.<sup>12</sup> Sundram and Shantaveer documents 80 patients of intracranial fungal granuloma during their study period of 19 years.<sup>16</sup> Male predominance was seen in our study, 60% patients were males in our study with males to female ratio of 3:2. Similar trend is seen other international studies.<sup>16</sup>



The age incidence revealed that maximum number of patients were seen in 4<sup>th</sup> and 5<sup>th</sup> decade of life. Similar results are seen in other studies.<sup>16</sup>

The commonest etiology for fungal granuloma brain was paranasal sinus allergic or infective disease similar results are seen in other studies.<sup>20,21</sup> Mostly our patients were immunocompetent, although the major predisposing illness was allergic or infective involvement of paranasal sinuses. Badley and salzman detected 17 cases of fungal brain infection in organ transplant patients.<sup>7</sup> Similar results shown by Selby and Ramirez and by Hagensee and Bauwens.<sup>21,22</sup>

The common clinical features were pre existing nasal allergic infection disease, headache, vomiting, proptosis, alteration of vision involvement of cranial nerves and stroke like presentation were rare. Other studies also show similar clinical presentation.<sup>21,22</sup>

X-Ray PNS, CT scan for paranasal sinuses and brain were performed in almost all cases for the diagnosis of the disease. MRI brain was utilized for better evaluation of its spread to the skull base and brain. Other authors also utilized the same investigations for the diagnosis and evaluation of the disease for example.<sup>20-23</sup>

The treatment of the fungal granuloma was catered according to the anatomical spread of the disease. **Transethmoidal** approach was utilized to take the biopsy and maximum debulking of the granuloma from ethmoidal air cells spreading to the skull base or adjacent areas. This approach is very effective, easy and safe for the disease is limited to ethmoidal air cells or adjacent area. This approach had been utilized so many other surgeons both ENT and Neurosurgeons.<sup>26,27</sup>

**Combined approaches** like maxillotomy and transcranial approach can be utilized in the same sitting if the fungal granuloma had involved the maxillary sinus with retromaxillary spread to the infraorbital area, optic nerve and anterior or middle skull base areas. The utilization of combined approaches had been recently introduced by the author.<sup>26,27</sup>

**Surgical excision** of fungal granuloma had been performed by many neurosurgeons but results are not encouraging and had high mortality.<sup>24</sup>

**Bur hole Biopsy** was performed to confirm the presence / absence of fungal granuloma brain, where nasal sinuses were not involved and MRI / CT pictures were not sufficient for final diagnosis. We performed Bur Hole Biopsy in 7 cases. Two cases survived one revealed excellent recovery while one showed some

morbidity and result was fair. While in craniotomy and excision group only one patient survived out of 5, too had morbidity and result was labeled as “fair”. The mortality in Bur Hole Biopsy sub group was 71% while mortality in sub group craniotomy and excision was 80%. In group B, where fungal granuloma had involved Nasal sinuses and brain parenchyma only endonasal clearance of fungal granuloma was performed by ENT department in 6 cases. No surgical procedure was performed for brain fungal granuloma i.e. managed conservatively. Among these 6 cases one had excellent result treated by new magic drug “VORICONAZOLE” one case also revealed good response by prolonged use of and Amphotecian B for 2 months followed by oral SPORONOX more than 1 year and patient is still tabing this drug. Third patient recovered but had multiple hospitalization due to recurrence of fit etc. His result was labeled as fair 3 patients put of 6 died (50%) mortality which is still better than 2 sub groups of Bur hole Biopsy and surgical excision respectively. Other studies also shows high mortality with brain fungal granuloma.

If surgical excision is performed, these patients had the tendency to deteriorate during the end of first post operative week. This deterioration is usually due to vasculitis and brain edema. Hence these patients should be subjected for elective hyperventilation if patient just start to become confused or drowsy. The hyper ventilation for 7 – 10 days can be very effective for the treatment of brain swelling. Hyperventilation is recommended in all conditions of raised intracranial pressure.

In our study in few case craniotomy was performed for excision of tumour (suspecision of meningioma) with no evidence of PNS involvement, in such situation, we send the piece of tumour for fungal hyphae staining. The specimen was sent in Normal saline for staining in formaline mixed solution for the specimen to be subjected for detail histopathology, once the presence of fungal hyphae staining is confirmed, the antifungal treatment should be started immediately. We gave injection Amphotericin B in all cases except 1 case in which variconazole was administrated to the patient. The results of VARICONAZOLE were excellent. Initial dose Variconazole is 2 to 4 ampules as infusion mixed with 5% D/W followed by 1 ampule of Variconazole Twice a day for 3 – 4 weeks followed by capsule VARICONAZOLE mg twice a day for about 6 months or till the disease is eliminated. The drug is a new very effective drug but it is expensive and its availability is limited in Pakistan. Many authors had

recommended the use of "VARICONAZLE" as the drug of choice for fungal infection.<sup>24,25</sup> The general metabolic condition of the patient should be kept in mind and associated diabetes myelitis, hypertension, chronic liver disease. Renal disease, which ever if present should be treated with consultation of concern consultant. Proper feeding, fluid and electrolyte imbalance, proteins especially albumin deficiency should be treated efficiently. Interferon therapy and amino-acid replacement should be done to improve the general immunity of the patient, when indicated. These factors had been stressed by other authors as well in the management of serious diseases.

Our study revealed high mortality and morbidity due to fungal brain infection, the mortality rare was our study Similarly high mortality had been reported by many authors.

## CONCLUSION

No single modality of treatment can be utilized for all cases of fungal granuloma brain. The treatment modality is selected depending upon the anatomical structures involved. Following surgical approaches can be utilized when extra cranial compartment had fungal granuloma.

1. Transethmoidal approach for fungal infection involving Ethmoidal, sphenoidal air cells and its adjacent structures including skull base.
2. Maxillotomy in combination with transcranial approaches had good results for removal of the fungal granuloma when it is yet extradural. It is especially used for big maxillary fungal granuloma causing proptosis due to its spread to the retro orbital and anterior skull base regain extradurally.
3. Bur hole Biopsy can be performed to confirm the diagnosis, nasal sinuses are not involved and the nature of disease is to be ascertained for presence or absence of fungal granuloma brain.
4. If the nasal sinus nasal sinuses, nasal cavity is involved alongwith spread of fungal granuloma through the dura matter to the brain parenchyma then only endonasal procedure to clear the fungal granuloma no surgery should be perform for brain parenchymal fungal granuloma. It should be treated by anti fungal, anti allergic drugs. If patient can afford the expensive treatment "VARICONAZOLE" should be utilized for excellent results.

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