ORIGINAL ARTICLE

Fungal Infections of the Central Nervous System in the Seemingly Immunocompetent – common or unusual

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Abstract

Objective
To identify and describe characteristics of invasive Central Nervous System [CNS] fungal infections including their clinical presentation, diagnosis, treatment and outcome at our center.

Methods
This is a retrospective study design using secondary data analysis. Medical records of patients with CNS fungal infections presenting during an eight-year period, from June 2011 to June 2018 were reviewed to determine patients' baseline characteristics (age, gender, comorbidities), site of infection in brain, clinical presentation, imaging findings, medications used and response to treatment including mortality.

Results
Twenty-one patients with invasive CNS fungal infection were identified and reviewed. A majority of patients were men (81%). The clinical presentation was variable and most patients presented with more than one feature. Headache was the commonest symptom and was seen in 67% of the patients. Response to treatment was better in patients with Aspergillosis (71.4%) as compared to other organisms (43%). The overall response rate of CNS fungal infections was 62%. Overall mortality in these patients was 24%. Voriconazole is better tolerated while Amphotericin B deoxycholate use was associated with expected kidney injury. Surgical excision at any time during the treatment was associated with better response.

Conclusion
The results of present study show that CNS fungal infections cause significant mortality. The index of suspicion should be high even in immunocompetent patients presenting with headache, facial swelling or neurological involvement. Prompt and accurate diagnosis and early treatment should be instituted to avoid disease progression and mortality. There is a need for better tolerated drugs (Liposomal Amphotericin B and Posaconazole) to be available at low cost. Surgery should be considered as a treatment option wherever feasible.

Key words
CNS – Central nervous system

Introduction

Fungal infections contribute to high disease burden including Pakistan. These infections are under diagnosed due to insufficient diagnosing modalities and lack of index of suspicion.[1,2] Invasive fungal infections and candidemia has poor outcomes. Invasive fungal infections are common in diabetics and in immunocompromised patients but also reported to occur in substantial numbers in overtly immunocompetent hosts. Involvement of CNS in invasive fungal infection is less common but is a diagnostic and treatment challenge and carries poor outcomes.[1,2,3]

Common fungi that can cause disease in CNS include Aspergillus, Zygomycetes, Cryptococcus and Candida species. Such infections may be more commonly seen in tropical climates.[4] They can present as meningitis or can form brain abscesses.[5] Cerebral fungal infections occur due to extension of infection from contiguous structures (paranasal sinuses, mastoid, middle ear cells), hematogenous spread or via direct invasion during neurosurgical procedures or trauma. Sino-orbital Aspergillosis is emerging infection in Asia, Africa and Middle East making it a common cause of contiguous spread to CNS. Infections from paranasal sinuses usually extend to frontal lobe of brain and those from middle ear and mastoid air cells involve the temporal lobes.[2,4]

There are no characteristic clinical or laboratory parameters to diagnose cerebral fungal infection. Diagnosis of CNS fungal infections relies mainly on radiological findings, histopathology and culture. CSF examination has limited yield in diagnosing cerebral aspergillosis however it can help in identifying fungal

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meningitis.[5,6] Findings of CNS fungal infections on MRI and CT scan are variable and can present as a intra/extra parenchymal solid mass lesion (with or without mass effect, infarct, haemorrhage), abscess, meningeal enhancement or mucosal thickening of sinuses and as bone erosions.[7]

Serological tests (galactomannan antigen and Beta D glucan) on blood or CSF can support the diagnosis of CNS fungal infection. Galactomannan is used for invasive aspergillosis and Beta D glucan is detected in patients with mold or yeast infections. Tissue sampling for histopathology and culture is ultimately required in many cases for exact diagnosis and identification of fungal species.[8]

Various drugs are used to treat invasive fungal infections including amphotericin B, triazoles, echinocandins and 5-flucytosine. Echinocandins have little penetration in brain. The course of treatment is often complicated due to inappropriate diagnostic tests, side effects of treatment, resistance and cost issues.[8,9,10,11] Outcome is better when surgery is combined with medical treatment.[12]

To date there are very few studies to evaluate presentation, treatment and outcome of CNS fungal infections in Pakistan. Invasive fungal infection remains challenging due to diagnostic delays and inappropriate treatment. The rationale of this study is to highlight the clinical and radiological characteristics and outcome of this serious disease in our country.

Patient and Methods

Study design and settings

A retrospective review was performed of all the patients, who were diagnosed with CNS fungal infections from June, 2011 to June, 2018, after approval from institutional review board. A total of 21 patients were identified and included in this study using the keyword CNS fungal infection to search in the hospital's electronic database. The demographics, age, risk factors, clinical presentation, investigations, drugs and surgical options were assessed in addition to the associated outcome and mortality.

Inclusion / Exclusion criteria

We included patients with the diagnosis of CNS fungal infections, from June 2011 to June 2018, based on biopsy result or radiological findings suggestive of CNS fungal infections in with supportive clinical evidence. Patients with meningitis are excluded from this study.

Patient characteristics

The baseline characteristics of the patients including age and treatment duration were recorded as quantitative variables. The gender, associated comorbidities, clinical findings, biopsy results, type of surgical intervention, response to treatment and side effects were recorded as qualitative variables.

Definitions

Confirmed CNS fungal infection is defined as diagnostic histopathology or culture results.
Suspected fungal infection is defined as mass lesion on MRI that was treated as fungal infection but biopsy not done.

Response was defined as improvement in both symptoms and radiological findings in clinical follow up over 6 months.

No response was defined as no improvement in either symptoms or radiological findings in clinical follow up over 6 months.

Disease progression was defined as progression in either baseline symptoms or radiological signs in clinic follow up over 6 months.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software (version 20.0; SPSS, Chicago, IL, USA). Continuous variables were stated as Mean ± SD and categorical variables were computed as frequencies and percentages.

Results

Descriptive statistics

Out of 21 patients, 20 (87.5%) patients were adults and one was of pediatric age group; mean age was 34.88 ± 19.49 years. Seventeen (81%) patients were men. Comorbidities were present in 12 (57%) patients while 9 (43%) patients had no comorbid illness. Four patients had cancer (Hodgkin's lymphoma in three and nasopharyngeal cancer in one patient). Four patients were diabetics and two of them had chronic sinusitis as well. Chronic sinusitis was also present in two other patients without diabetes. One patient had ischemic heart disease and another was using long term steroids for dermatitis. Location of home cities of patients is illustrated in figure 1.

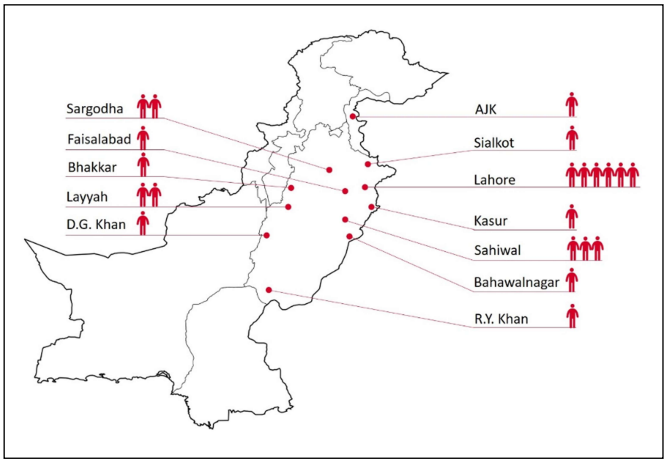

Fig.1 Demographic presentation of patients with CNS fungal infection

Clinical presentation (represented in table 1) was variable and most of our patients had more than one presenting symptoms. Biopsy was done in 19 (90%) patients; surgical excision was done in 10 (47.6%) patients. Surgical procedures are detailed in table 2. MRI (Magnetic resonance imagining) findings also remained variable and are elaborated in table 3.

Table 1: Clinical presentation of patients with CNS Fungal infections

Clinical Presentation	No. of patients
Headache/facial pain	14
Focal deficit	
Facial Numbness	2
Decreased vision/ cranial nerve palsy	8
Limb weakness	5
Slurred speech	1
Orbital swelling/proptosis	6
Nasal blockade	5
Altered mental status/memory loss	4
Seizures	3
Fever	3

Table 2: Details of surgical procedures

Procedure	No. of patients
Excision	5
Biopsy	7
Trans-sphenoidal biopsy/ Nasal sinus biopsy / debridement	6
Biopsy of cervical node/ neck sinus	1
None	2

Table 3: MRI Brain findings

Findings	No. of patients
Mass lesion in brain	
Mass lesion with no complications	3
Mass lesion in brain with complications (mass effect/ infarcts)	4
Ring enhancing lesion with meningeal enhancement/mass effect	3
Sinuses/ mastoid/orbit infection with intracranial extension	8
Skull based osteomyelitis with intracranial extension	1
Gliomatosis cerebri with mass effect	2

MR spectroscopy was done in 4 patients suggestive of glial tumor in two, glioma in one and meningioma in another patient. Cultures were available in only 6 patients. Three of them showed no growth, one patient had mixed growth of Mucormycosis and Aspergillus, one had Aspergillus and another had Fonsecaea species grown in culture. Histopathology result and diagnosis made, is shown in table 4. Site of fungal infection within the brain is described in figure 2.

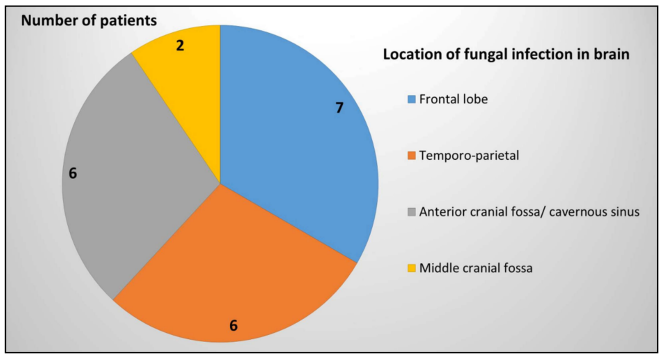

Fig 2. Location of CNS fungal infections

Response to treatment

Response was described by analyzing patients in two groups. The first group was CNS aspergillosis who received voriconazole and the second group was CNS fungal infections other than aspergillosis who were treated with Amphotericin B deoxycholate or Posaconazole. Response was determined after clinical and radiological review. Mean duration of treatment was calculated in both groups. The number of patients who had undergone surgical excision was also documented.

Fourteen patients were treated as CNS Aspergillosis. Twelve patients had confirmed while two had suspected CNS Aspergillosis. All patients were treated with voriconazole. Details about response in patients with CNS aspergillosis and patients who had fungal infections other than aspergillus is given in table 5.

Side effects of medical therapy

In patients treated with voriconazole, adverse events were seen in 3 out of 14 (21.4%) patients. One patient developed drug associated rash and visual symptoms occurred in 2 patients requiring stopping of voriconazole at 4 months in one of them.

Out of seven patients who were given Amphotericin B, 5 (71.4%) developed acute kidney injury.

Discussion

In this retrospective analysis, we have presented the clinico-radiological features, treatment and outcome of 21 patients with CNS fungal infection. In our study 14 patients belong from southern Punjab, which may be a noteworthy point when patients present with CNS complaints from these districts.

Table 4: Histopathology of patients with CNS fungal infections

Histopathology	Number of patients	Diagnosis n
Septate fungal hyphae with necrotizing granulom atous inflammation	7 (33%)	Aspergillosis 7
Septate fungal hyphae with non necrotizing granulomatous inflammation	4 (19%)	Aspergillosis 3 Fonsecaea spp. 1
Septate fungal hyphae with inflammation / no granuloma	2 (9.5%)	Aspergillosis 2
Non septate fungal hyphae with inflammation	4 (19%)	Mucormycosis 1
Non septate hyphae with necrotizing granuloma	1 (4.7)	Mucormycosis 1
Necrotizing granuloma with mixed infection	1 (4.7%)	Polymicrobial infection 1 (Aspergillus and Mucor)
Not identified	2 (9.5%)	Aspergillosis 2

Table 5: Response in patients with CNS aspergillosis and CNS fungal infections other than Aspergillosis

Diagnosis	Mean Duration of Voriconazole treatment in days	Surgical excision	Clinical response	Radiological response	Over all response	Disease Progression	Mortality
Aspergillosis (14 patients)	227 ± 138 days	7 (50%)	10 (71.4%)	10 (71.4%)	10 (71.4%)	1 (7%)	3 (21.4%)
CNS fungal infections other than Aspergillosis							
Mucormycosis (5 patients)	126 ± 56.17	2	2	2	2	2	1
Fonsecaea (1 patient)	90	0	0	0	0	0	1
Mixed infection (1 patient)	335	1	1	1	1	0	0
Overall (7 patients)	151 ± 94.18	3	3	5	3 (42.8%)	2 (28.5%)	2 (28.5%)

However, this effect may be due to institutional referral bias.

To date most of the research suggested certain risk factors (cancer, diabetes, HIV, steroids, transplant, neurosurgery etc.) for invasive fungal infections[2,,10,13,14]. Our study highlights the occurrence of invasive fungal infections in previously healthy patients as 43% of studied patients had no conventional risk factor for CNS fungal infections. In the remainder, diabetes, chronic sinusitis and cancer were identified as risk factors for invasive fungal disease.

Patients of CNS fungal infections usually present with headache, fever, focal neurological deficit (including cranial neve palsies, visual loss), change in mental status, nasal blockade and ear

discharge.[16] Dubey *et al*. pointed out that patients of CNS fungal infections usually have more than one clinical complaint and headache was the most common presenting feature. Also, patients can present with neurological disturbances (including visual impairment and limb weakness), nasal blockade, and eye swelling, though fever and fits remained less common presentation. Similar to this study, our patients also present with more than one clinical feature and most common presenting feature was headache while fever and seizures were not common, consistent with the afore mentioned study.[12]

Most of the CNS fungal infections had predilection for frontal lobe followed by temporo-parietal lobes, anterior cranial fossa and middle cranial fossa however none of the patients had infection in posterior cranial fossa. [12]

Similar to Dubey *et al*., the most performed surgical procedure was craniotomy for excision/biopsy (12 out of 21 patients). However, 6 patients in our study required trans-sphenoidal biopsy, with or without debridement, twice the number mentioned by Dubey *et al*, where only 3 patients underwent this procedure.

As published in literature, MRI findings of CNS fungal infections in our study remained non-specific.[16,17] Radiological findings included mass lesion and ring enhancing lesion that can be complicated with mass effect and infarcts. MRI remained a helpful tool in revealing possible source of infection as 8 (38%) patients showed mucosal thickening of sinuses, orbital wall or mastoid as well, suggesting contiguous cause of intracranial disease. MRI of 2 patients showed gliomatosis cerebri, one had disease of both frontal lobes and the other had disease in tempro-parietal lobes.

Four patients of aspergillus granuloma had undergone MR spectroscopy (MRS), which failed to differentiate aspergilloma from possible glial tumor in two, glioma in one and meningioma in another patient. These results are consistent with the study of MRS that showed its inability to differentiate Aspergilloma from brain tumors and other infections.[18]

Sundaram *et al*. reviewed pathology of 130 cases of CNS fungal infections reported in Southern India.[4] He reported most common fungal infection in CNS was Aspergillus (56%) followed by Mucormycosis (30%). Our study revealed similar findings with 12 (57%) out of 21 patients showed thin branching septate fungal hyphae, with positive GMS and PAS stain, suggestive of aspergillosis. Out of these 12 patients, granuloma was found in 10 patients while 2 patients had only chronic inflammation without granuloma formation. In high TB burden countries like Pakistan its crucial to differentiate fungal granuloma from tuberculous. The second most common diagnosis based on histopathology was zygomycosis in 5 (23.8%) patients. One of the patients showed mixed infection with Aspergillus and Mucor, and another revealed Fonsecaea spp. The above mentioned study showed availability of cultures in only 29% patients, similar to our study where cultures were available in only 6 patients (28.5%). The reason of low numbers of culture requests was mainly biopsy done before referral to the ID physicians.[4]

Our study exhibited that fungal infections invade frontal lobe of brain in 33% of patients followed by temporo-parietal lobe in 28% of patients, anterior cranial fossa and cavernous sinus in 28% of patients and middle cranial fossa in 9.5%. None of the patient had fungal granuloma of posterior lobe and these findings are same as existing data.[12]

Schwartz *et al*. conducted study on 81 patients of probable or confirmed CNS Aspergillosis who were treated with voriconazole.[19] In this study response (complete, partial and stable disease) was seen in 50.6% and failure to therapy was reported in 49.3% of patients. Mortality due to CNS aspergillosis was 46%. Neurosurgical intervention was associated with better outcome.[19] In our study treatment for aspergillosis was given in 14 patients. All patients received voriconazole with mean duration of 227 +/- 138 days. The duration was determined by clinical judgement of response (clinical resolution of symptoms and radiologic improvement). Clinical and radiological response was seen in 10 (71.4%) patients that was better than the aforementioned study. Failure of therapy was seen in 3 (28.6%) patients. Disease progression was seen in one patient who had gliomatosis cerebri of both frontal lobes. He was advised re-biopsy but patient was lost to follow up. Three patients (21.4%) died in this group, that is lower than that reported by Schwartz *et al*. The reason of this difference could be the fact that majority of patients included in aforementioned study were immunocompromised and had undergone organ/stem cell transplant while in our study most of the patients were immunocompetent. In our study surgical excision of diseased tissue was done in 7 patients and all of these 7 patients survived, highlighting that surgical intervention at any time during the course of illness may cause better survival.

A study done on mucormycosis showed response in only 37% of patients with mucormycosis and out of 41 patients who died, 41 (87%) died due to mucormycosis.[20] In our study of CNS fungal infection other than aspergillosis, combined clinical and radiological response remained low i.e. 3 out of 7 (42.8%) patients and failure of treatment was observed in remaining 4 (57.2%) patients. Three patients with treatment failure had mucormycosis, one of whom died and the other two had disease progression till their last follow up. Spellberg *et al*. showed surgical debridement in patients who had mucormycosis is related with good outcome[21]. In our study two patients of mucormycosis had surgical debridement, and both showed disease progression. Possible reason of disease progression could be the treatment interruption in both patients due to Amphotericin B intolerability, non-access to Posaconazole, unavailability of liposomal Amphotericin B and additionally superadded bacterial infection leading to skull-base osteomyelitis

in one of them. Both of these patients were also diabetics.

Voriconazole was well-tolerated in our population with side effects seen in only 3 (21.4%) patients, better than existing literature that reports adverse events in 39.5% of patients treated with voriconazole.[19] In our study Amphotericin B deoxycholate was poorly tolerated with 5 out of 7 (71.4%) patients developing acute kidney injury at some point requiring intermittent discontinuation of drug. This is higher than reported nephrotoxicity of Amphotericin B i.e. 50%.[22] Studies showed that liposomal Amphotericin B has better tolerability than non liposomal Amphotericin B and former is associated with survival rate of 67% as compared to only 39% with later one.[21,22]

Conclusion

The results of our study showed that mortality in CNS fungal infections especially those other than aspergillosis is high. Consideration to this diagnosis should be made even in immunocompetent patients presenting with headache, facial swelling or neurological involvement. Prompt and accurate diagnosis with tissue biopsy for histopathology and culture should be attempted as all septate hyphae should not be considered as a confirmed diagnosis of aspergillosis and voriconazole may not be the best option in such cases. Early treatment should be done to avoid disease progression and mortality. Drugs with better tolerability (Liposomal Amphotericin B and Posaconazole) are required to be available at low cost. Surgery should be opted as a treatment option, of CNS fungal infections, wherever feasible.

Limitations

This study has various limitations including use of retrospective data and lack of availability of culture data since in many instances the patients were referred to us after surgery and only histopathology was available.

References

1. Jabeen K, Farooqi J, Mirza S, Denning D, Zafar A. Serious fungal infections in Pakistan. Eur *J Clin Microbio & Inf Dis* 2017 Jun 1;36(6): 949-56.
2. Chakrabarti A, Chatterjee SS, Das A, Shivaprakash MR. Invasive aspergillosis in developing countries. Medical mycology. 2011 Apr 1;49(Supplement_1):S35-47.
3. Shamim MS, Enam SA, Ali R, Anwar S. Craniocerebral aspergillosis: a review of advances in diagnosis and management. *J Pak Medi Assoc* 2010;60(7):573.
4. Sundaram C, Umabala P, Laxmi V, Purohit AK, Prasad VS, Panigrahi M, Sahu BP, Sarathi MV, Kaul S, Borghain R, Meena AK. Pathology of fungal infections of the central nervous system: 17 years' experience from Southern India. *Histopathology* 2006 Oct;49(4):396-405.
5. Scully EP, Baden LR, Katz JT. Fungal brain infections. *Current opinion in neurology* 2008 Jun 1;21(3):347-52.
6. Ruhnke M, Kofla G, Otto K, Schwartz S. CNS aspergillosis. CNS drugs. 2007 Aug 1;21(8):659-76.
7. Jain KK, Mittal SK, Kumar S, Gupta RK. Imaging features of central nervous system fungal infections. *Neurology India* 2007 Jul 1;55(3):241
8. Mattiuzzi G, Giles FJ. Management of intracranial fungal infections in patients with haematological malignancies. *British journal of haematology* 2005 Nov;131(3):287-300.
9. Mousset S, Buchheidt D, Heinz W, Ruhnke M, Cornely OA, Egerer G, Krüger W, Link H, Neumann S, Ostermann H, Panse J. Treatment of invasive fungal infections in cancer patients—updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Annals of hematology* 2014 Jan 1;93(1):13-32.
10. Mukherjee PK, Sheehan DJ, Hitchcock CA, Ghannoum MA. Combination treatment of invasive fungal infections. *Clinical microbiology reviews* 2005 Jan 1;18(1):163-94.
11. Black KE, Baden LR. Fungal infections of the CNS. *CNS drugs* 2007 Apr 1;21(4):293-318.
12. Dubey A, Patwardhan RV, Sampth S, Santosh V, Kolluri S, Nanda A. Intracranial fungal granuloma: analysis of 40 patients and review of the literature. *Surgical neurology* 2005 Mar 1;63(3):254-60.
13. Ramesha KN, Kate MP, Kesavadas C, Radhakrishnan VV, Nair S, Thomas SV. Fungal infections of the central nervous system in HIV-negative patients: experience from a tertiary referral center of South India. *Annals of Indian Academy of Neurology* 2010 Apr;13(2):112.
14. Zarrin M, Zarei Mahmoudabadi A. Central nervous system fungal infections; a review article. *Jundishapur Journal of Microbiology*. 2010;3(2):41-7.
15. Panackal AA, Williamson PR. Fungal infections of the central nervous system. Continuum: Lifelong Learning in Neurology. 2015 Dec 1;21(6, Neuroinfectious Disease):1662-78.
16. Jain KK, Mittal SK, Kumar S, Gupta RK. Imaging features of central nervous system fungal infections. *Neurology India* 2007 Jul 1;55(3):241.
17. Hilary LP, Mcwilliams S, Mellnick VM, Lubner MG, Pickhardt PJ, Menias CO. Imaging Spectrum of Invasive Fungal and Fungal-like Infections 1.
18. Gupta RK, Jobanputra KJ, Yadav A. MR spectroscopy in brain infections. *Neuroimaging Clinics* 2013 Aug 1;23(3):475-98.
19. Schwartz S, Ruhnke M, Ribaud P, Corey L, Driscoll T, Cornely OA, Schuler U, Lutsar I, Troke P, Thiel E. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood* 2005 Oct 15;106(8):2641-5.
20. Pagano L, Offidani M, Fianchi L, Nosari A, Candoni A, Picardi M, Corvatta L, D'Antonio D, Girmenia C, Martino P, Del Favero A. Mucormycosis in hematologic patients. *Haematologica* 2004 Jan 1;89(2):207-14.
21. Spellberg B, Ibrahim AS. Recent advances in the treatment of mucormycosis. *Current infectious disease reports* 2010 Nov 1;12(6):423-9.
22. Dupont B. Overview of the lipid formulations of amphotericin B. *Journal of Antimicrobial Chemotherapy* 2002 Jan 1;49(1):31-6.