Fungal infections of the nervous system: Current perspective and controversies in management

Rewati Raman Sharma*

National Neurosurgical Centre, Khoula Hospital, PO Box-90, Postal Code-116, Muscat, Oman

**Abstract**

In the last two decades, more elaborative use of intensive care units for serious medical disorders, advancements in transplant procedures and concomitant use of immunosuppressive therapies as well as the pandemic spread of HIV, etc. have increased the incidence of systemic fungal infections, especially life threatening central nervous system (CNS) infections.

The CNS fungal infections present with various clinical syndromes: meningitis; encephalitis; hydrocephalus/raised intracranial pressure (raised ICP); space occupying lesions; orbito-rhino-cerebral syndromes; acute cerebro-vascular events and spinal infections. However, the common presentations among these ones are basal meningitis, hydrocephalus, space occupying lesions (cerebral abscesses and granulomas) and stroke syndromes. Clinical picture may mimic tubercular meningitis and therefore, needs careful evaluation.

The CNS mycoses carry higher risks of morbidities and mortality as compared to other infective processes and therefore promptly require precise diagnosis and appropriate medical and/or surgical management strategies to optimize the outcome.

Among the antifungal drugs, the Amphotericin B had remained first line of therapy for many decades in invasive fungal infections but is not effective in many forms of mycoses. Fortunately, many useful antifungal drugs were introduced during the last two decades. Initially, the lipid based formulations of the Amphotericin B, then the new triazoles and most recently, echinocandins. These medications are used more frequently in combinations. Initial experiences are encouraging in favor of their useful roles in the management of invasive fungal infections. But still, many questions are unanswered and controversies persist relating to their selection and use.

1. Introduction

Fungal infections of the central nervous system (CNS) are rare clinical entities presenting with protean clinical manifestations, difficult diagnostic dilemmas and special therapeutic challenges. Most fungi have low pathogenicity and therefore rarely infect normal subjects. Contrary to this in recent times, the incidence of opportunistic CNS mycosis has greatly increased especially in immunocompromised hosts such as patients with sepsis, prolonged ventilation, oncological therapies, organ transplants, extensive use of antibiotics, HIV, etc.

The CNS fungal infections may present with various clinical syndromes which may be specific for certain fungi. Among these, common syndromes are basal meningitis, hydrocephalus, space occupying lesions (such as cerebral abscesses, granulomas, etc.) stroke syndromes (aspergillosis, zygomycosis) and spinal infections. In general, symptomatic CNS fungal infection carries higher risks of morbidities and mortality as compared to viral, bacterial, or parasitic CNS disorders. An early recognition and an appropriate medical and surgical management strategies are therefore of paramount importance in improving the overall prognosis in CNS mycosis.

Still Amphotericin B remained as one of the most useful broad spectrum antifungal medication but with many toxic side effects and limitations. Fortunately, during the last two decades, many useful antifungal drugs were introduced. Initially, the lipid based formulations of the Amphotericin B, then the new triazoles and most recently, echinocandins. These medications are used more effectively in combinations. Initial experiences are in favor of their useful roles in the management of invasive fungal infections. But still, many questions are unanswered and controversies are persisting in relation to their selection and use.
2. Historical aspects

Generally, Hippocrates is credited with the first description of candidiasis in his book—"epidemics", in which he described white patches in the oral cavity of a debilitated patient. The fungal etiology of these thrushes was established in 1840s by Berg and Bennett. Zenkar described the first case of intracerebral candidiasis that had died in 1861. In 1792 in his book, Micheli (a priest and botanist) described Aspergillus to refer to the nine species that microscopically resembled to aspergillus, a perforated globe frequently used to sprinkle holy water during religious ceremonies. However, it was Oppe (1897) who reported the first case of rhino-orbital-cerebral aspergillosis. First case of human zygomycetes infection was described by Kurchenmeister in 1855 who isolated non-septate hyphae from a cancerous lung. In 1943, Gregory described in detail three cases of rhino-cerebral zygomycosis. In 1888, Nocard described an aerobic acid fast actinomycete in cattle and Eppinger in 1891 reported the first case of metastatic (from lung) cerebral nocardiosis.

Coccidioidomycosis was first reported by Alejandro Posadas and Robert Wernicke in 1892 and in 1905 Ophuls described first case of coccidioidal meningitis. Blastomycosis by Gilchrist (1894), Histoplasmosis by Darling (1906), and coccidioidomycosis (South American Blastomycosis) by Adolfo Lutz in 1908 in Brazil were well described. Cryptococcus was reported initially by Buses in 1894 and later by Fuglmen in 1901.Gonyea reported three patients with blastomycosis meningitis in 1978.

Many advances have been made in the diagnostic armamentarium of the fungal infections. Medical advancements paralleled increase in fungal infections as a result of medical therapy of various diseases and have produced many more cases of immunocompromised status which are prone to opportunistic systemic mycosis.

3. Epidemiology and classification

Fungal infections are not notifiable diseases and precise information on their prevalence through out the world is not available. Although, in general, fungi are cited to be ubiquitous; however, some forms have a more restricted geographical distribution than others. More than 100 thousand fungal species are recognized by some forms have a more restricted geographical distribution than others. More than 100 thousand fungal species are recognized by humans. Fortunately, only about 10–15% of pathological fungi usually produce systemic/CNS mycosis. True pathogenic fungi (having a restricted geographic distribution, mostly in USA) are Blastomyces, Coccidioides, Paracoccidioides, Histoplasma, Sporothrix, etc. They produce clinical lesions in normal individuals and then provide long term immunity to the patients recovered from the active infections. Whereas the opportunistic fungi (having ubiquitous distribution) are Aspergillus fumigatus, Candida albicans, Cryptococcus neoformans, Rhizopus arrhizus, etc. and these provide no long term immunity to the patients and hence relapses are noted.

Fungi presents mainly in three forms: moulds (colonies of branching hyphae-mycelium), yeasts (colonies of single cells) and intermediate forms. Some fungi are thermomorphogenic changing their forms from mould to yeast under different environmental conditions. Clinically important true pathogenic dimorphic fungi are Blastomyces, Coccidioides, Histoplasma, Sporotrichum and Paracoccidioides. Cryptococcus remains as an encapsulated yeast in all environmental conditions.

Fungi are broadly classified in three major groups as follows:

1. Pseudo-mycetes/yeast—Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Paracoccidioides, Sporotrichum

2. Septate mycetes—Aspergillus, Cephalosporium, Cladosporium, Diplorhinotrichum, Hormonendrum, Paeclomycyes, Penicillium

3. Non-septate mycetes—Absidia, Basidiobolus, Cunninghamhamella, Mucor, Rhizopus

Usually, the inhaled aerosolized fungi initiate a primary mycotic infection in the lungs and or paranasal sinuses which is usually self-limiting but may spread to other organs. Frequently, hematogenous dissemination (from lungs, intestine or prosthetic heart valves) results in the systemic mycosis and less frequently fungal infections appear in the CNS.

Direct contiguous spread to the CNS occurs from the paranasal sinuses, orbits, retro-mastoid region and retro-pharyngeal area in some patients. Direct implantation may result during the period of trauma, intensive care procedures and intracranial operations. Identifying the etiological agent as fungal and not bacterial is vital since antibacterial therapy is not effective against fungi and CNS mycoses lead to high morbidity and mortality. Actinomycetes are bacteria with narrow branched vegetative cells that superficially resemble fungi. The common ones belong to Nocardia (aerobic) and Actinomycyes (anaerobic) species and therefore, these are also considered here in this write-up.

4. Pathogenesis

Fungi profoundly grow in the environment with abundance of organic matter and water. The enzymes produced by the fungi act on the organic matter and break down their protein, carbohydrates and other macromolecules into micro-molecules which are then easily used by the fungi to maintain their life processes.

Generally, the CNS is regarded as immunological privileged site. The brain has a specialized, relatively impermeable blood brain barrier (BBB) and its surrounding sub-arachnoid spaces also have effective meningeal barriers. These highly vascular structures provide effective resistance to fungal infections. For immune surveillance, mainly activated T-lymphocytes are usually permitted across the BBB in normal individual. However in immune-compromised states these anatomical and functional barriers are easily overcome by common (opportunistic and or pathogenic) fungi to produce clinical manifestations.

Fungal infections of the CNS also evoke humoral and cellular responses as in bacterial infections with the scope to enable the host to eliminate the pathogen. Activation of the resident brain cells by fungi combined with relative expression of immune-enhancing and immune-suppressing cytokines and chemokines which may play a determinant role and partially explain the immunopathogenesis of CNS fungal infections. Activated resident brain cells such as microglia, astrocytes and endothelial cells express major histocompatibility complex (MHC) Class I and Class II molecules and therefore act as antigen presenting cells. In addition, they express complement receptors and produce cytokines, chemokines and molecules with antifungal activity such as nitric oxide (NO). They are also capable of phagocytosis. Microglia acting as antigen presenting cells stimulates T-cell proliferation and cytokine secretion which in turn stimulate these microglial cells to ingest and more effectively kill invading fungi. The complement (C) system is a key component of innate immune system, playing a central role in host defense against pathogens. It is also a powerful drive to initiate inflammation and if unregulated can result in pathological changes leading to severe tissue damage. It is generally accepted that the C system is essential to mediate cytolysis of fungi. Furthermore, it is well known that C-receptors expressed by activated microglial cells are important to mediate phagocytosis. Immunopathogenesis of CNS fungal infections in humans is not completely understood. The
exploration of the genomic sequence of most fungal pathogens can help better understand pathogenesis, virulence and immune response of host defense against these pathogens. Further studies in these areas will advance our understanding about CNS mycoses.

5. Clinical syndromes of the CNS fungal infections

The CNS fungal infections usually result from pulmonary, intestinal, cardiac, or craniofacial mycoses and therefore intracranial seedlings occur either during hematogenous dissemination or by direct extension from the juxta-cranial sites. The CNS mycosis may be disseminated (cryptococcosis, coccidioidomycosis, etc.), focal (aspergillosis, zygomycosis, etc.), or multifocal (candidiasis). Fungi produce diseases due to their allergenicity, toxigenicity, pathogenicity, neurotoxicity and/or virulence. Fungi producing distinctive clinical syndromes are found in three major morphological forms:

1. Small pseudomyecetes (yeasts) causing leptomeningitis: Because of their small size (cryptococcosis, blastomycosis, histoplasmosis, coccidioidomycosis, etc.) these fungi gain access to the cerebral microcirculation. From there they seed and infect the CSF and its containing leptomeninges. Fungi may reach the brain parenchyma along the Virchow Robin spaces around the penetrating and perforating small cortical/cerebral vessels arising from the major vessels in the sub-arachnoid spaces. Therefore, these fungi may result in meningitis and or meningo-encephalitis (Fig. 1).

2. Large pseudomyecetes (candidiasis) producing cerebral abscesses and granulomas: These fungi are larger than 20 microns and can occlude cerebral arterioles. Such occlusions lead to focal cerebral ischemia and infarctions. Depending upon the virulence of the fungi and host resistance, variety of the cerebral fungal lesions appear such as ischemic areas, focal infarctions, cerebritis, abscesses, granulomas and combinations of these lesions. The tissue necrosis and highly virulent fungal infection rapidly convert infected cerebral areas into micro-abscesses. Whereas a good host resistance but persistence of infection causes granulomatous inflammatory reactions in adjacent leptomeninges, neural parenchyma or in both sites. This may result in hydrocephalus which needs to be treated promptly (Fig. 2).

3. Septate (aspergillosis) and non-septate (zygomycosis) mycetes are very large in size and normally grow with large branched hyphae. Usually they infect juxta-cranial sites (paranasal sinuses, orbits, oral cavity, etc.) for a considerable period of time and then are capable of invading contiguous cranial bones, meningeal tissues, basal cerebral venous sinuses, etc. as well as intermediate and large sized intracranial arteries, and result in arterial thrombosis and occlusions which in turn causes extensive cerebral infarctions. These patients clinically present as the cases of cerebral stroke. The evolving hemorrhagic cerebral infarct is then converted to septic infarcts with associated cerebritis and abscesses whereas a good host defense result in granuloma formation.

**Based on the aforementioned facts, the clinical presentations of the CNS fungal infections, either alone or in combination, are as follows:** Meningitis; encephalitis; raised intracranial pressure (raised ICP); mass effect producing parenchymal space occupying lesions (cerebral cysts, abscesses, granulomas, etc.), orbito-rhino-cerebral syndromes; acute cerebro-vascular events such as ischemic or hemorrhagic strokes producing vascular syndromes and spinal fungal infections. However, common presentations among these are basal meningitis, space occupying lesions (cerebral abscesses and granulomas) and hydrocephalus.

---

**Fig. 1.** A T1 weighted axial MR image following contrast infusion, in a well diagnosed case of cryptococcal meningitis, showing small multiple enhancing areas in the white matter in both the cerebral hemispheres representing foci of cryptococcal infection.

**Fig. 2.** A Computed Topographic axial scan in a diagnosed case of extensive paranasal sinusitis and sino-cranial aspergillosis showing a hyper-attenuation granulomatous lesion in the right thalamo-mesencephalic region causing hydrocephalus with periventricular lucencies.
5.1. Meningeal syndromes

Meningitis, meningo-encephalitis and hydrocephalus: Chronic fungal meningitis is common, whereas subacute menin gitis relatively less common, and the acute fungal meningitis distinctively rare except in ICU patients or prolonged ventilatory patients with severely immunocompromised states. Most of the pseudomycet (yeasts) are capable of producing menin gitis or meningo-encephalitis. Clinical features of fungal meningitis and meningo-encephalitis usually are headaches, nausea, vomiting, visual impairment, and papilledema and later neck stiffness with fever, personality changes, and then seizures; deterioration in sensorium, cranial nerve palsies and hydrocephalus. In many patients, there are no focal or generalized physical signs.

Fungal meningitis ranges from the relatively common crypto cocal meningitis to the rare meningitis due to large pseudomy cetes (dimorphic) or filamentous (septate and non-septate) fungi. Therefore, the fungal meningitis more frequently occurs with Cryptococcus, Coccidioides, Blastomyces, Paracoccidioides, Sporothricum, Histoplasma and Candida as compared to Filamentous fungi such as Aspergillus, Cladosporium (Phaeohyphomycosis) and Zygomycetes.

CNS Cryptococcal infection (European Blastomycosis) usually presents with typical clinical features of meningitis (subacute or chronic) or meningo-encephalitis. Acute fatal meningitis is rare in cryptococcosis; but the periods of remissions and relapses are well known. Cryptococcosis is one of the most common CNS fungal infections in immunocompromised patients. Nearly one tenth of the patients with HIV develop cryptococcosis and in significant number of patients, cryptococcosis manifests as an initial presentation of HIV infection.

Coccidioides is probably the most virulent of the fungi causing human fungal infections. Meningeal inflammation due to fungal infection results in accumulation of exudates, opacification of leptomeninges and obliteration of sulci with caseous granulomatous nodules at the base of the brain and in the cervical region. Extensive fibrosis causes obstructive hydrocephalus and invasion of blood vessels leads to multiple aneurysms. Unusually large granulomatous lesion and frank abscesses may occur in the brain and spinal cord.

In autopsy studies, the most common cerebral mycosis is caused by candidiasis. Candida albicans originally infects the oral cavity and esophagus usually following prolonged antibiotic treatment, then invades sub mucosal blood vessels and finally disseminates hematogenously to the CNS. Candida also reaches CNS via colonization of the ventricular drains, shunt tubing and central venous lines. Therefore, Candidal meningitis can occur spontaneously as a complication of disseminated candidiasis or as a complication of an infected wound or ventriculostomy via direct inoculation of the organism into the CNS. Usually chronic but infrequently subacute, basal fungal meningitis causes obliteration of intracranial subarachnoid spaces and results in increased intracranial pressure with or without hydrocephalus. All the other major fungi (i.e., histoplasmosis, phaeohyphomycosis, and aspergillosis) can also produce life threatening meningitis and therefore high index of suspicion, prompt diagnosis and vigorous therapies are required to reduce morbidities and mortality. In our combined series of 170 patients of CNS fungal infections, six out of 10 patients with CNS candidiasis and all 21 cases of cryptococcosis had presented primarily with clinical features of meningitis or meningo-encephalitis; however, meningitis as a secondarily associated feature was also seen to be coexisting with other primary CNS manifestations in our cases of blastomycosis, coccidioidomycosis, aspergillosis, cladosporium, zygomycosis, nocardiosis and actinomycosis. Cryptococcal and candidial meningitis usually respond well to intravenous Amphoterin B therapy with or without flucytosine. In refractory case of candidiasis, lipid formulations of Amphoterin B, triazoles and echinocandins are used. Fluconazole is used as a maintenance therapy in cryptococcal meningitis in AIDS patients. Triazoles and Amphotericin B are used against common fungal pathogens with favorable outcome.

5.2. Intracranial fungal space occupying lesions

Intracranial granulomas, abscesses and cysts, especially in the intraparenchymal locations, form the bulk of the intracranial fungal space occupying lesions (Sols). Clinically, fungal granulomas are more frequently diagnosed as compared to fungal abscesses and in many cases, a mixed picture is seen. Intraparenchymal cysts occur commonly in basal ganglia in cryptococcal infection as compared to other mycoses.

Candidiasis, aspergillosis, cryptococcosis, cladosporiosis, mucormycosis, etc. commonly produce CNS fungal abscesses (Fig. 3). Fungi disseminating hematogenously from an extra cranial site cause multiple areas of infection within the brain. Initially, the meningo-encephalitis occurs with vasculitis-thrombosis and late hemorrhagic cerebral infarction develops and then an abscess forms. Abscess forming organisms may progress in a fulminant fashion leading rapidly to death (Fig. 4). Extremely preterm neonates and patients with definitive immunological deficiency syndromes/states are at high risk of developing these complications with high morbidities and mortality. Unfortunately in many cases, the diagnosis of these lesions is revealed only at autopsy (Figs. 5–7).

CNS fungal granulomas are commonly produced by aspergil llosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, cladosporiosis, mucormycosis, cryptococcosis, etc. Aspergillosis and mucormycosis of the paranasal sinuses infect the subjacent meninges and brain parenchyma to produce frontal and temporal granulomas whereas hematogenous spread of other fungi from elsewhere produce piaeval granulomas in general. Clinical symptomatology depends on fungal infection at the primary location, the
site of brain lesion as well as associated meningitis, edema and mass effect, etc. Fungal granulomas may resemble tuberculomas except that they have a more fibrous consistency. Intraparenchymal cerebral cysts in the basal ganglia sometimes develop in patients with cryptococcosis (Fig. 8). In our series of 170 cases, 29 cases had intracerebral abscesses, 58 cases of cranial & intracranial granulomas and 13 cases of intra-parenchymatous cryptococcal cysts. About 70 patients with primary presentations of the SOL were subjected to surgical procedures with overall poor prognosis although it has improved recently due to aggressive interventions and combination antifungal medications.

Small fungal SOLs are managed with aggressive antifungal medications and supportive care whereas significantly large lesions...
may also need conventional, stereotactic or ultrasound guided surgical interventions. Prognosis depends on the prompt recognition and management of the life threatening condition.

5.3. Orbito-rhino-cerebral & skull base syndromes

Fungal infections involving the nasal cavities, paranasal sinuses, orbits, cranial bones and mandible may extend to cranial and intracranial structures especially basifrontal and basitemporal areas (Fig. 9). Long standing fungal sinusitis due to invasive fungi i.e., Aspergillus, Cladosporium, Zygomycetes (mucormycosis) as well as fungus like bacteria such as Actinomycetes and Nocardia, etc. are mainly responsible. Diabetic ketoacidosis is the most common predisposing factor. According to the involvement of the anatomical structures (paranasal sinuses, orbits optic nerves, cranial bone penetration with involvement of intracranial space and the brain parenchyma) in the skull base region, many types and combinations of clinical syndromes are named: sino-cranial (commonest), sino-orbital, sino-orbito-cranial, orbito-cranial, cavernous sinus, orbital apex, purely orbital syndromes and more extensive orbito-rhino-cerebral syndromes with associated specific and non-specific symptoms and signs (Fig. 10). Some patients present purely with cranial mono- or poly-neuropathy. Each patient must be clinico-radiologically assessed according to his symptomatology to define the anatomical extent of the fungal involvement.

Control of diabetes, radical surgical procedures to the orbit and paranasal sinuses, neurosurgical intervention for intracranial infection and aggressive antifungal drug therapy including irrigation of aerated paranasal sinuses with antifungal agents are needed. Excision of necrotic and infected tissues as well as the drainage of paranasal sinuses is needed in these patients.

Control of diabetes, radical surgical procedures to the orbit and paranasal sinuses, neurosurgical intervention for intracranial infection and aggressive antifungal drug therapy including irrigation of aerated paranasal sinuses with antifungal agents are needed. Excision of necrotic and infected tissues as well as the drainage of paranasal sinuses is needed in these patients.
5.4. Acute cerebro-vascular events

In CNS fungal infections, acute cerebro-vascular events take the form of either ischemic (commonly) or hemorrhagic (uncommonly) strokes. Aspergillus, Zygomycetes, Candida, Coccidioides, Histoplasma, Cryptococcus, Penicillium, etc. are all known fungal infections rarely presenting with acute cerebro-vascular events. Gradual contiguous involvement of the skull base structures in cases of prolonged paranasal fungal sinusitis (commonly aspergillosis, zygomycosis, cladosporiasis, etc.) leads to angio-invasion which in turn results in fungal vasculitis and thereafter the thrombotic occlusions occur in the major branches of the cerebral vasculature at the skull base: internal carotid arteries and/or vertebro-basilar system. The hyphae invade the vessel walls causing cerebral arterial thrombosis, cerebral infarction and cerebritis (Fig. 11). The evolving hemorrhagic infarcts may convert into septic infarcts.

In cases of major cerebral fungal arteritis in which the direct surgery is inappropriate, reliance has to be placed on the antifungal antibiotics and supportive therapy. In our series of 170 patients, there were 45 cases of major cerebral artery thrombosis especially either in the ICA or Basilar artery. Ischemic cerebral strokes also result due to cardiac-emboli in patients with fungal endocarditis. Organisms frequently involved in fungal endocarditis are Candida, Aspergillosis, etc. However, Candida is the most common causative organism of fungal endocarditis in both, immuno-competent and immunocompromised patients. Rarely, disseminated fungal cardiac-emboli lodging in the peripheral cerebral vasculature leads to intracranial fungal mycotic aneurysms, solitary or multiple, which may present with extremely rare and usually fatal complications of sub-arachnoid hemorrhage/intracerebral hemorrhage with and without cerebral infarctions. Intracranial fungal mycotic aneurysms in the proximal cerebral vasculature (internal carotid vessels and vertebro-basilar branches) usually result from the fungal angio-invasion in cases of long standing fungal sinusitis (aspergillosis, zygomyosis, coccidioidomycosis, etc.). We had six cases of mycotic aneurysms in our series of 170 cases. Apart from antifungal drug therapy and supportive treatment, if a peripheral cerebral aneurysm is recognized, it should be excised whenever possible. However, a direct surgical treatment is usually not possible in proximal cerebral fungal aneurysms except rarely endovascular therapy, surgical trapping or peripheral ligation. In general, the outlook is extremely poor for these patients with CNS fungal infections presenting with acute strokes.

5.5. Spinal fungal infections

Spinal fungal infections are relatively rare entities and occur usually in immune-compromised patients and only occasionally in immune-competent subjects (Fig. 12). These lesions closely mimic mycobacterial infections and should be considered in the differential diagnoses of the osteolytic, granulomatous and/or abscess producing lesions of the spine. The differentiation must be made using hematological tests including ESR, skin testing (Montoux test, coccidioidal skin test, etc.), blood cultures, serologic testing (i.e., serum anticoccidioidal IgG CFA titer above 1:32), positive cytology, cultures and histo-pathological examinations of the biopsy specimens, neuro-imaging along with clinical history, etc. Majority of the destructive lesions usually affect middle/centre of the vertebral bodies. However, in cases of spinal tuberculosis the posterior elements are commonly spared whereas in fungal infections (aspergillosis, blastomycosis, coccidioidomycosis), all spinal elements may be involved. Spinal column may be affected from upper cervical to the sacral region; however, upper thoracic level of the spine is most commonly affected by contiguous spread of the fungal lesions in the lungs (endemic respiratory fungal pathogens — Aspergillus, Blastomyces, Coccidioides,) and uncommonly involved due to hematogenous spread (Aspergillus, Candida albicans). Fungal infections of the spine may present as intradural, extradural and/or vertebral lesions.

Spinal intradural involvement usually occurs as a part of generalized cerebro-spinal fungal leptomeningitis but other intradural lesions are extremely rare such as localized spinal meningitis, spinal arachnoiditis [(aspergillosis, cryptococcosis) presenting as radiculopathy and or myeloradiculopathy] and fungal myelitis. Progressive myelopathic syndromes may be due to mass effect.
producing compressive spinal lesions such as granulomas, intramedullary abscess (Candida albicans), etc. The management primarily depends on the antifungal drug therapy in these patients and in only some cases of granulomas/abscesses, where indicated, neurosurgical decompression is needed.

Extradural and vertebral lesions are relatively more frequent than the intradural lesions and tend to occur usually in patients with immune-compromised states (severe systemic disorders with malnutrition, immune-suppression and organ transplants, HIV infection, systemic malignancy, uncontrolled diabetes mellitus, alcohol or intravenous drug abuse, long term antibiotic therapy or corticosteroid uses and prolonged parenteral nutrition). Hematogenous dissemination of fungal infections causes constitutional symptoms of fever, headache, malaise, anorexia, night sweats, lethargy, musculoskeletal pains, etc.

In critically ill patients from infancy to old age needing invasive interventions in the intensive care units, candidiasis is emerging as a frequently diagnosed nosocomial infection due to hematogenous dissemination with high morbidities and mortality. Aspergillosis is also a frequent opportunistic infection (look for chronic paranasal sinusitis) in such cases with impaired immunity. Blastomycosis is predominantly a granulomatous cutaneous (look for cutaneous fistulae) or respiratory infection and then spreads systemically. Coccidioidomycosis (Modeling Valley Fever) primarily causes benign mildly symptomatic inhalational (arthroconidia in the dust in endemic areas) pulmonary lesions. However, in about 5–10% cases, especially in patients with compromised cell mediated immunity (such as AIDS, organ transplants with immunosuppressants, Hodgkin’s disease, collagen vascular diseases, etc.), CNS, spinal and musculoskeletal systems are secondarily involved (look for the nodular skin lesions and osteolytic skull lesions on the plain X-rays). Multifocal spinal destructive lesions are common with para-vertebral involvement (granuloma and abscess formation) especially in the lower thoracic and upper lumbar regions.

Plain X-rays of the spine show osteolytic, spinal deformities and instability as well as soft tissue shadow of the paraspinous abscesses and granulomas. The spinal CT scan demonstrates the findings seen on the plain X-rays more clearly as well as shows the surrounding soft tissue involvement more precisely. MRI scans of the fungal spondylitis (aspergillosis/candidiasis, etc.) show discal hypointensity with relative preservation of the intra-nuclear cleft on T2 weighted images, as compared to hyper intensity of the intervertebral discs with loss of intra-nuclear cleft in pyogenic spondylitis in these images. In general, fungal and tubercular granulomatous lesions cause more pronounced destructive vertebral lesions with relative sparing of the intervertebral discs in the initial stages of infection whereas the pyogenic infection destroys, both, the vertebral bodies and the discs. In our series of 170 cases, seven patients had spinal syndrome and 3 patients has fungal craniospinal osteomyelitis. Once the fungal infection establishes within the spine, initially the destruction of the vertebral occurs quite rapidly and then the intervertebral discs are involved. Multilevel spinal lesions, spinal column deformities, significant para-vertebral lesions, fungal lesions at junctional regions, spinal cord deformation/compression and progressive neurological deficits are frequent consequences needing active neurosurgical management. Neurosurgical armamentarium is consisting of percutaneous CT guided biopsy, operative debridement of the infected tissues, excision of the granulomatous lesions, drainage of abscesses, fusion-reconstructions in cases of spinal destructive deformities and stabilization with instrumentations in patients with spinal instabilities to maintain a normal vertebral alignment along with the antifungal drug therapy and supportive care. Overall prognosis is far better as compared to intracranial fungal infections.

6. Antifungal drug therapy and controversies

In the last two decades, more elaborate use of intensive care units (neonatal and adult) for various serious medical disorders, advancements in transplant procedures and concomitant use of immunosuppressive therapies as well as endemic spread of HIV, etc. have certainly increased the incidence of systemic fungal infections especially life threatening or lethal CNS fungal infections. Reliance only on Amphotericin B was not effective. Fortunately, during the same period, many useful antifungal drugs were discovered and introduced. Initially, the lipid based formulations of the Amphotericin B, then the new triazoles and most recently, echinocandins. These medications are used, more and more in combinations, in seriously ill patients with invasive mycoses. Now evidence based data are gathering together in favor of their important roles in the management of invasive fungal infections. But still there are many unanswered questions and controversies relating to their use. Unquestionably, CNS fungal infections pose serious challenges in their management with controversies surrounding their medical and surgical therapies. Surgical options are less controversial in cases of focal or localized superficial cortico-subcutical lesions (such as abscesses and granulomas) in the non-eloquent areas of the brain. Whereas invasive multifocal lesions, deep cerebral and or brain stem lesions, focal lesions rapidly spreading to involve large parts of the brain and major vascular invasions are usually not surgically amenable or curable. Reliance has to be placed heavily on the antifungal drug therapy along with appropriate surgical options where indicated. Recent advances in antifungal pharmacotherapy are attempting to provide drugs with their greater efficacy and lesser toxicity especially in such invasive CNS fungal infection. Evidence based studies (using new drugs, singly or in combination) are accumulating and are assuming greater roles in the management of these serious infections. Currently following classes of natural and synthetic antifungal drugs are commonly used:

1. Polyenes: Amphotericin B Deoxycholate Complex (Fungizone registered, Bristol-Myers Squibb), Nystatin
   Lipid formulations of Amphotericin B:
   a) AmBisome,
   b) Amphocil (Amphotericin B colloidal dispersion (cholesteryl sulfate), ABCD)
   c) Abelcet (Amphotericin B lipid complex, ABLC)

2. Pyrimidines: 5-fluorocytosine (Flucytosine)

3. Triazole drugs: Fluconazole, Itraconazole, Posaconazole, Voriconazole

4. Echinocandins: Caspofungin, Anidulafungin, Micafungin

5. Miscellaneous: Imidazoles (Clotrimazole, Ketoconazole, etc.), Oral polyenes (Amphotericin, Nystatin), Griseofulvin, etc. for dermal, oro-pharyngeal, esophageal, intestinal and vaginal infections. Terbinafine is effective for nail and ring worm infections.

Amphotericin is the broad spectrum antifungal drug active against most fungi: moulds and yeasts. Being a Polyene drug, it is usually not absorbed through the gastrointestinal tract and is mainly given intravenously after a test dose (intravenous infusion of 1 mg over 30 min) before the first therapeutic dose (at least 30 min of observation period) to prevent anaphylactic reaction. In the blood circulation, it is highly protein bound with less penetration in the tissues and body fluids hence behaves like a highly toxic substance with profound nephrotoxicity.

Lipid formulations of Amphotericin are less protein bound with more tissue penetration and are less toxic with lesser infusion related as well as renal side effects. However their clinical
indications as well as efficacies are nearly same as Amphotericin and are 8–10 times more costly. In patients with pre-existing renal dysfunctions, obviously, lipid formulations are preferably advised but same is not justified in patients with normal renal functions. For life threatening invasive fungal infections (aspergillosis, zygomycosis, etc.), lipid formulations are initially advised. These medications are indicated for systemic candidiasis, cryptococcosis and the endemic mycoses (blastomycosis, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis). In these infections, Amphotericin B and triazole antifungals such as Voriconazole, Fluconazole, and Posaconazole are advised either singly or in combinations.

Flucytosine (5-fluorocytosine) is the only commonly used drug (usually in combination with Amphotericin B) among the pyrimidine class of antifungal drugs especially in infections such as invasive candidiasis, cryptococcosis, aspergillosis, etc. with significant bone marrow toxicity, hepato-toxicity and drug resistance.

Among the azole group of antifungal medications, imidazole (miconazole, ketoconazole) are commonly used for localized surface infections and triazoles (itraconazole—for dermatophytes only), fluconazole, voriconazole, posaconazole are used for invasive life threatening fungal infections because of their ease of administration (oral preparations), high bioavailability, water solubility, low protein binding and a good body fluid distribution, relatively low toxicity and long half-life. A good CSF penetration is usually achieved. Triazoles have a relatively broad spectrum of activity against common fungal pathogens e.g., Aspergillus, Blastomyces, Candida, Cryptococcus, Coccioides, Paracoccidioides, Histoplasma, etc. However, their limitations lie in the interactions with co-administered drugs, development of the resistance of fungal organisms (Candida) especially with fluconazole and hepatitis toxicity. Most recently introduced antifungal drugs are Echinocandins (Caspofungin, Anidulafungin, Micafungin) which are showing promising results in combination antifungal therapy in the serious opportunistic invasive fungal infections (candidiasis and aspergillosis (caspofungin only)). There is a high risk of fungal infections in immunocompromised patients i.e., long term care in ICUs (intensive care units), HIV, renal transplant with immunosuppressants, etc. Prophylactic antifungal drug therapy using oral azoles (fluconazole, itraconazole, ketoconazole) is given in such cases. Fluconazole is the drug of choice for long term use. If fungal infection is confirmed then the Amphotericin is used initially on empirical basis. Once the type of the opportunistic fungal infection is established then the more specific antifungal drugs are given: Candidiasis (Triazoles, Echinocandins), Cryptococcosis (Amphotericin and Flucytosine in synergistic combination), Aspergillosis (Amphotericin, Voriconazole, Posaconazole, Caspofungin), Mucormycosis (Amphotericin), etc. Caspofungin is licensed for the empirical treatment of systemic fungal infections (Candida, Aspergillus, etc) with neutropenia. Fluconazole is often used in prevention of the relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy.

There are many unanswered questions related to the management of CNS fungal infections and their medications. Therefore management controversies are abounding and the available data do not provide satisfactory answers to questions and controversies. The factors which play important roles in genesis of these controversies are reported to be personal preferences and experiences of the treating physicians. There are many pertinent questions such as follows: 1.Is Amphotericin B still be the first line of antifungal therapy in severely ill immunocompromised patients with CNS mycoses?; 2.Are lipid formulations of Amphotericin more effective therapeutically than the Amphotericin B itself?; 3.Which lipid formulation is better for which type of fungal infection?; 4.Has total effective therapeutic daily dose of lipid formulations defined?; 5.Are triazoles replacing Amphotericin B or its lipid formulations? and 6. Echinocandins are more effective when prescribed singly or perform better in combination therapy? There are many questions and controversies ranging from the choice of antifungal medications in CNS mycoses to calculation of their doses, and the route of administration as well as effective therapeutic combinations. Only further research and evidence based data will help resolve these questions and many more controversies in the management of the CNS fungal infections in future.

7. Conclusions

Fortunately fungal infections of the CNS are rare as compared to bacterial and viral infections; however, recently there is an increase in such infections following relative increase in immunocompromised patient population due to apparent reasons. The CNS fungal infections present with various clinical syndromes which may be specific for certain fungi: meningitis, encephalitis, hydrocephalus/raised intracranial pressure; mass effect producing space occupying lesions (cerebral cysts, abscesses, granulomas, etc.); orito-rhino-cerebral syndromes; acute cerebro-vascular events and spinal fungal infections. The common presentations among these are basal meningitis and or hydrocephalus, space occupying lesions (cerebral abscesses and granulomas) and stroke syndromes. Clinical picture may mimic tubercular meningitis and need careful evaluation. The CNS mycosis carries higher risks of morbidities and mortality as compared to other infective processes and therefore promptly requires precise diagnosis and appropriate medical and or surgical management strategies to optimize the outcomes. Amphotericin B remained a bench mark medication for such infection. Many useful antifungal drugs, however, were introduced during the last two decades. Initially, the lipid based formulations of the Amphotericin B, then the new triazoles and most recently, echinocandins. These medications are used more frequently in combinations. Now evidence based data are gathering together in favor of their usefulness in the management of invasive fungal infections. But still, many questions are unanswered and controversies persist relating to their selection and use. Further research and evidence based data will help resolve these questions and many more controversies in the management of the CNS fungal infections in future.

Conflict of interest
None to be declared.

Funding
None.

Ethical approval
None.

References
31. Edwards JE.
23. 
29. Basra R, Barada G, Ojaimi N, Khalaf RA. Susceptibility of
17. Wiles CM, Mackenzie DWR. Fungal diseases of the central nervous system. In:
20. Dotis J, Roilides E. Immunopathogenesis of central nervous system fungal
35. Miller DJ. Diagnosis and management of
e2. Choi HY, Jackson IT. Rhinocerebral mucormycosis combined with brain abscess. 
19. 
81. 
54. 
78. DiNubile MJ, Strohmaier KM, Lupinacci RJ, Meibohm AR, Sable CA, 
76. Wagner DK, Varkey B, Sheth NK, DaMert GJ. Epidural abscess, vertebral
55. Hedges TR, Leung LS. Parasellar and orbital apex syndrome caused by aspergillosis. 
53. Hedges TR, Leung LS. Parasellar and orbital apex syndrome caused by aspergillosis. 
32. 
57. 
60. Ho CL, Deruytter MJ. CNS aspergillosis with mycotic aneurysm, cerebral
56. Weprin BE, Hall WA, Goodman J, Adams GL. Long term survival in rhinocerebral
50. 
85. 
43. 
154. 
74. Lu DC, Wang V, Chou D. The use of allograft or autograft and expandable titanium
58. 
63. 
62. 
47. 
102. 
73. 
24. 
72. Khazim RM, Debnath UK, Fares Y. 
70. 
69. 
45. Mischel PS, Vinters HV. Coccidioidomycosis of the central nervous system: 
46. 
48. 
51. 
52. 
53. 
49. 
50. 
77. 
88. 
42. Choi HY, Jackson JT. Rhinocerebral mucormycosis combined with brain abscess. 
41. 
38. 
59. 
e2. Choi HY, Jackson IT. Rhinocerebral mucormycosis combined with brain abscess. 
10. Kirkpatrick JB. Neurologic infections due to bacteria, fungi and parasites. In: 
11. Kissane JM, editor. 
40. 
34. 
71. 
75. 
79. 
83. 
78. 
79. 
66. 
67. 
68. 
70. 
71. 
72. 
73. 
74. 
75. 
76. 
77. 
78. 
79. 
80. 
81. 
82. 
83. 
84. 
85. 
86. 
87. 
88. 
89. 
90. 