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Central nervous system infections in immunocompromised patients

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ABSTRACT

Purpose of review: Although rare, central nervous system (CNS) infections are increasingly being recognized in immunocompromised patients. The goal of the present review is to provide a practical diagnostic approach for the intensivist, and to briefly discuss some of the most prevalent conditions.

Recent findings: Immunocompromised patients presenting with new neurological symptoms should always be suspected of a CNS infection. These infections carry a poor prognosis, especially if intracranial hypertension, severely altered mental status, or seizures are present. Clinical examination and serum blood tests should be followed by brain imaging, and when no contra-indications are present, a lumbar puncture including cerebrospinal fluid PCR to identify causative organisms. Empirical therapy depends on the type of immunodeficiency. In HIV-infected patients, the most common CNS infection is cerebral toxoplasmosis, whereas in other immunocompromised patients, aspergillosis, cryptococcal meningitis, and tuberculous meningitis are more prevalent. Multiple pathogens can be detected in up to 15% of patients. The diagnostic value of fast multiplex PCR has yet to be evaluated in this setting.

Summary: CNS infections represent a rare but severe complication in immunocompromised patients. A systematic approach including early diagnosis, appropriate antimicrobial treatment, early ICU admission and aggressive measures to reduce intracranial pressure may improve outcome.

INTRODUCTION

Opportunistic central nervous system (CNS) infections often necessitate admission to an intensive care unit (ICU), mainly because of altered mental status, seizures or medical complications. In addition, these infections are associated with significant morbidity and mortality. Over the past decades, the population of immunocompromised patients has increased. Reasons for this phenomenon are, amongst others, the successes of transplantation management, improvements in the management of hematological cancer patients, and the use of new immunosuppressive drugs in patients with autoimmune diseases. The likelihood that critical care physicians will encounter those patients and admit them to their units is growing. The present review discusses the epidemiology of severe CNS infections in the immunocompromised, with a major emphasis on HIV-infected patients, solid organ transplant recipients, and hematological / cancer patients. The goal is to update the general intensivist or neuro-intensivist with a practical diagnostic approach, and to briefly discuss some of the most prevalent conditions.

EPIDEMIOLOGY

The epidemiology of CNS opportunistic infections differs, depending on the type and etiology of immunosuppression. In HIV-infected individuals, the introduction of combination antiretroviral therapy (cART) in 1996 reduced the overall incidence of common CNS opportunistic infections, from 13.1 per 1000 patients-years in 1996-97 to 1.0 per 1000 patients-years in 2006-2007 in Europe (1). In a single-center study conducted in 210 HIV-infected patients admitted to the ICU with neurological complications between 2001 and 2007, AIDS-defining conditions accounted for 42% of the ICU admission diagnoses (2). The three most prevalent opportunistic infections were cerebral toxoplasmosis, tuberculous meningitis and cryptococcal meningitis. These infections typically occur when the CD4-cell count is less than 200 cells per microliter. Data on prognosis of immunocompromised patients with neurological complications, specifically for the ICU, are scarce. Even in high-income countries with widespread access to cART, these CNS opportunistic infections still carry a poor prognosis, with 1-year survival rates 80-85% for cerebral toxoplasmosis and cryptococcal meningitis, and 52% for progressive multifocal leukoencephalopathy (PML) (3). In a study conducted in patients with HIV, presence of coma at admission was independently associated with ICU mortality, irrespective of the underlying infectious diagnosis (4). In another study, presence of intracranial hypertension at ICU admission was the only modifiable factor independently associated with ICU mortality (5). A multicenter study conducted in 100 HIV-infected patients with cerebral toxoplasmosis admitted to the ICU found that neurological outcome, as assessed by a modified Rankin score of 0-2 at 90 days, was favorable for 50% of patients. Independent predictors of poor outcome in this population included a lower CD4-cell count and coma at presentation (6).

In patients using chronic immunosuppressant therapy after solid organ transplantation or for other reasons, opportunistic infections depend on the level of immunosuppression and typically occur within 1 year following transplantation. Most frequent etiologies include CNS aspergillosis (approximate incidence, 0.2%), cryptococcal meningitis (0.1%), endemic fungi (0.2%), other molds including *Mucorales* (0.04%), PML (0.03%), and *Nocardia* (<0.01%) (7). In a single center study conducted in consecutive heart transplant recipients, CNS infections were diagnosed in 3% of patients, occurring within 4 years following transplantation (8). Development of CNS infection and seizures had an independent impact on long-term mortality (9).

Hematological cancer patients probably have the highest risk of CNS infections, mainly in the phase after allogeneic stem cell transplantation (allo-SCT), but also at other stages in their disease process, as a result of the primary disease, or in the leucopenic phase after chemotherapy. Older studies have reported an incidence of up to 15 % in the induction phase before, or after allo-SCT (10-13). In a recent Japanese case series, the cumulative incidence of CNS infection after allo-SCT was 4.1% at 1 year and 5.5% at 5 years, with a significantly worse survival in those patients (14). Another recent Italian case series reported an overall incidence of 6.6% neurological complications after allo-SCT, of which 30% were of infectious origin (15).

Severe bacterial meningitis can occur in immunocompromised patients. In patients with HIV, the incidence is 8-fold higher as compared with the general population, with similar clinical signs and outcome (16). In solid organ transplant patients, the incidence is 7-fold higher as compared with the general population and causative pathogens include *Streptococcus pneumoniae*, and Gram-negative bacilli (17). In allo-SCT patients, the incidence is 40 cases / 100000 patients per year (30-fold higher compared with other persons) and the most common causative organism is *Streptococcus pneumoniae* (18).

DIAGNOSTIC APPROACH

The diagnosis of CNS infection should be based on a systematic approach, including clinical signs, temporal evolution, brain imaging features, and CSF analysis. If bacterial meningitis is suspected, blood cultures should be drawn and antibiotics started immediately. Experts recommend that brain imaging should be performed before LP in all severely immunocompromised patients presenting with a suspicion of CNS infection (19). A brain MRI is the radiologic modality of choice to detect early ischemic lesions, small parenchymal lesions, and brain inflammation (20). In patients with hemodynamic instability or non-MRI compatible equipment, a CT-scan with contrast remains a good alternative, notably to rule out intracranial complications requiring additional invasive therapy, i.e. brain abscess, hydrocephalus or cerebral empyema. A recent study conducted in 363 episodes of suspected CNS infection, including 45% of immunocompromised patients, found that the diagnostic accuracy of clinical signs and blood tests to rule out CNS infection was low. This study

suggested that CSF leukocytosis was the best parameter to differentiate any CNS infection versus other diagnosis (2). The diagnostic workup is challenging, and several points need to be considered:

- Clinical signs and symptoms of CNS infections in immunocompromised patients may be confounded by the effects of immunosuppressive therapy itself, or by the presence of renal or hepatic failure and associated metabolic disturbances and/or drug accumulation. Of note, fever may be absent.
- In HIV-infected individuals, the risk of CNS opportunistic infection depends on the CD4-cell count and is low in patients with more than 200 CD4-cell count /mm³.
- In transplant recipients, the peak period for opportunistic infections affecting the CNS is 1–6 months after transplant (7).
- Daily low dose cotrimoxazole prophylaxis may not provide full prevention from common CNS infections (including *L. monocytogenes*, *T. gondii*, and *Nocardia* species) (21).
- Multiple viral CNS infections can be detected in up to 15% of patients, suggesting that a systematic diagnostic work up, largely based on serum and CSF analysis, is mandatory (**Table**) (12). If safe and feasible, CSF analysis should screen all relevant pathogens (20, 22). Detection of *T. gondii* by PCR in CSF has high specificity, but low sensitivity (50%), leading to high-rate of false negative (22, 23).
- A brain biopsy should be discussed for HIV-infected patients who fail to respond to specific anti-Toxoplasma therapy or in patients presenting with focal lesion(s) with significant mass effect and risk of brain herniation. Earlier biopsy should be strongly considered in atypical presentation with negative serology (23). In patients with hematological disorders or in solid organ transplant recipients, stereotactic brain biopsy/neurosurgical resection of brain lesions followed by identification and resistance testing of causative organism should be discussed in all patients presenting with focal parenchymatous abnormalities (e.g. brain abscess), without extra-neurological involvement (24).
- Tapering immunosuppression should be systematically discussed, especially in case of severe bacterial or fungal CNS infections.

BRAIN ABSCESS

Cerebral toxoplasmosis

Cerebral toxoplasmosis is caused by the protozoan *Toxoplasma gondii*, because of reactivation of latent tissue cysts. The most common presentation of *T. gondii* infection is (multi)-focal CNS syndrome with headache, altered mental status (67%), status epilepticus (22%), and/or focal deficit (59%), whereas fever is inconstantly found (median temperature 37.7°C, interquartile range, 37.0 - 38.5 °C) (6). Extra-neurologic features, (i.e. retinochoroiditis, pneumonia, and disseminated disease with multiorgan failure) are rare in patients with AIDS, but are frequently observed in hematological, cancer and transplant recipients (25). Brain imaging typically shows multiple ring-enhancing lesions in the grey matter of the cortex or basal ganglia, with associated edema and mass effect. The differential diagnosis of focal neurological disease in patients with AIDS most often includes primary CNS lymphoma and progressive multifocal leucoencephalopathy (PML). In the absence of immune reconstitution inflammatory syndrome, PML lesions typically involve white matter rather than gray matter, are non-contrast enhancing, and produce no mass effect. Most clinicians initially still rely on an empiric diagnosis, which can be established as an objective clinical and radiological response, to specific anti-*T. gondii* therapy. The standard therapy is pyrimethamine, sulfadiazine, and folinic acid, and is equally effective that the alternative trimethoprim-sulfamethoxazole can be used as an alternative (26). Increasing the CD4 count through effective cART therapy is of utmost importance.

Aspergillosis

CNS aspergillosis is one of the most common CNS opportunistic infections in solid organ transplant or hematological patients, but is rare in HIV (7). It usually results in brain abscess formation, or more rarely in cerebral infarction, with or without hemorrhage or meningitis. MRI typically may show ring-enhanced lesions, infarction and vascular infiltration from adjacent lesions. PCR or galactomannan might be useful for the diagnosis (24). CSF galactomannan will be positive in up to 90% of aspergillus meningitis, even when fungal cultures are positive in only 30%. Moreover, CSF fungal cultures are usually negative in patients with CNS infections other than meningitis (27). Voriconazole is the drug of choice in CNS aspergillosis. Alternatives are high doses of liposomal amphotericin B, and data on the effectiveness of echinocandins are scarce (28). Although corticosteroids can reduce mass effect and brain edema, they might be deleterious and should be avoided whenever possible. Neurosurgical removal of infarcted brain areas with poor drug penetration will facilitate definitive diagnosis and may contribute to outcome (24, 29).

Other etiologies

Many other microorganisms can cause brain abscess in immunocompromised patients, including *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Mucorales*, *Scedosporium*, and *Nocardia*. Nocardiosis is a rare opportunistic infection, mainly affecting solid organ transplant recipients. A recent multicenter study identified five factors independently associated with nocardiosis in this population, namely high calcineurin trough levels in the month before diagnosis, use of tacrolimus, corticosteroid dose, patient age, and duration of ICU stay after transplant (21). Among *Nocardia* species, *Nocardia farcinica* was the most frequent pathogen associated with brain infections. As the antibiotic susceptibility pattern varies among species, the antimicrobial regimen before species identification should rely on the association of antibiotics active on all species of *Nocardia*.

MENINGOENCEPHALITIS

Cryptococcosis

Most cryptococcal infections are caused by *Cryptococcus neoformans*, and occasionally by *Cryptococcus gattii*. HIV-infected patients who have CD4 cell counts <100 cells/mm³ have the highest risk (23). Cryptococcosis commonly presents as subacute meningitis with or without secondary encephalopathic features, that are usually a result of increased intracranial pressure (ICP), presumably from impaired cerebrospinal fluid (CSF) resorption. The opening pressure in the CSF may be elevated, with pressure ≥ 18 cm H₂O occurring in more than 60% of patients (30). Cryptococcosis is frequently a disseminated disease, involving other organ systems as well. CSF analysis demonstrates mildly elevated protein levels, low-to-normal CSF glucose levels, and moderate lymphocytic pleocytosis. HIV-infected patients may have little CSF inflammation, but India ink staining and cultures of CSF demonstrates encapsulated yeast in 60% to 90% of cases. CSF cryptococcal antigen is usually positive in those patients. A recent randomized clinical trial also showed that the combination of amphotericin B deoxycholate (1.0 mg/kg/day) combined with flucytosine was associated with improved survival and more rapid sterilization of CSF compared to the same dose of amphotericin B without flucytosine (30). Lipid formulations of amphotericin B (3 to 4 mg/kg/day) are also effective and should be used in patients with clinically significant renal dysfunction during therapy. After 2 weeks of successful induction therapy (i.e. clinical improvement and a negative CSF culture after repeat lumbar puncture), amphotericin B and flucytosine can be discontinued and consolidation therapy initiated with fluconazole. In a recent randomized clinical trial, dexamethasone did not reduce mortality in HIV-associated cryptococcal meningitis but was associated with more adverse events and disability compared to placebo (31). Early ICP elevation (> 25 mm H₂O) following diagnosis is associated with mortality (32), and its diagnosis and management is of paramount importance. Most patients do well with serial lumbar punctures, as

recent data suggest that these measures could result in a 69% relative improvement in survival, regardless of initial ICP (33). Protocols using serial LP for ICP management in resource-limited settings suggest a reduction in mortality compared to historical controls (34). When required, shunting (preferably ventriculoperitoneal) may provide sustained relief from intracranial hypertension symptoms. The need for shunting is associated with female gender and elevated CSF cryptococcal antigen titers (35).

Tuberculous meningitis

The most common presentation include signs of meningitis, i.e. headache, fever, altered mental status. Focal signs and cranial nerve palsies are common at presentation. Pleocytosis with lymphocytic predominance, high protein levels and low glucose levels are the hallmark findings of CSF analysis in patients with TBM. However, this CSF profile is non-specific and predominance of polynuclear cells can be seen. New commercial molecular diagnostic tests, such as GeneXpert MTB/RIF, have an important role in tuberculous meningitis diagnosis, but as with all other available tests, they lack sensitivity and cannot rule out the disease (36, 37). Most common neuroimaging findings include meningeal enhancement, hydrocephalus, basal exsudates, infarcts and tuberculomas (38).

Treatment of TBM includes a four-drug regimen, with isoniazid, ethambutol, rifampin and pyrazinamide for an induction phase of 2 months. Newer intensified regimens combining fluoroquinolones with high dose rifampicin have been recently tested but were not associated with improved survival (39). After the induction phase, isoniazid and rifampin should be continued for 10 months (23). A recent Cochrane review support the use of adjunctive corticosteroids (Intravenous dexamethasone, 0.4 mg/kg/ day), with a reduced risk of death at least in the short term (40). However, corticosteroids may have no effect on the number of people who survive TBM with disabling neurological deficit. Moreover, the benefits in terms of reduced mortality in HIV-infected patients are uncertain. Good outcomes depend upon the careful management of the common complications and controlling intracranial pressure. Hydrocephalus is detected in up to 65% of patients at presentation and is independently associated with visual impairment, cranial nerve palsy and basal exsudates (41). Hyponatremia is one of the most common acute complications of TBM, occurring in 45% of patients. It is mainly due to cerebral salt wasting and related to the severity of TBM (42). Outcome of TBM patients requiring invasive mechanical ventilation is poor, with less than 30% survival at 3 months (43). However, indicators of outcome in critically ill patients have yet to be determined.

CONCLUSION

Although rare, opportunistic CNS infections in immunocompromised patients have a high morbidity and mortality. A systematic diagnostic workup is mandatory to establish the most likely diagnosis as soon as possible. In addition to early empirical or directed antibiotic therapy, aggressive treatment of complications such as intracranial hypertension could increase survival. In HIV patients, increasing the CD4 count through cART in order to restore normal immunity is important. In solid organ or allo-SCT patients the benefits of reducing immunosuppression should be balanced against the risk of losing the graft.

KEY POINTS

- Immunocompromised patients presenting with new neurological symptoms should always be suspected of an opportunistic central nervous system infection.
- The diagnostic work-up should be aimed at finding the causative agent, as well as determining the nature and degree of immunosuppression, and should include blood and CSF laboratory tests, blood and CSF microbiology, contrast brain imaging (MRI if feasible).
- Multiple opportunistic pathogens can be present, suggesting that a systematic diagnostic work up is mandatory
- Empirical treatment aimed at the most likely pathogens should be started early.
- In some cases, tapering or interrupting immunosuppressive therapy should be considered.

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