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Infections in the immunocompromised child

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Abstract
Prevention and management of opportunistic infections in children is particularly relevant in an era demonstrating an increased prevalence of immunocompromising conditions. The presence of an unusual organism which results in serious infection in a child should therefore always raise the consideration of immune compromise. The more common opportunistic infections have become easier to recognize in recent times due to improved awareness and more refined diagnostic testing. Targeted treatment is usually followed by long-term prophylactic medication. The impact of these conditions on patient outcome is of clear significance and certainly warrants further discussion.

Keywords Infection · Immunocompromised child

Introduction

Central nervous system (CNS) infections represent an increasing challenge in the management of immunocompromised children. The types of infection and their consequences usually reflect the nature and severity of the underlying immunodeficiency and the virulence of the organisms involved [1, 2]. The more common pathogens are easier to diagnosis and treat, whereas opportunistic infections are caused by more unusual microorganisms and tend to be more severe, longer lasting, and unpredictable, making management more complicated. Additional risk factors in immunocompromised patients include the presence of indwelling catheters, disruption of mucosal barriers, and the need for repeat surgery and adjunctive therapies [1, 3].

An underlying immunodeficiency should be considered when an unusual organism is identified as the pathogen. Immunocompromising conditions may be either congenital or acquired. *Congenital* conditions include B cell defects, T cell defects, combined B cell and T cell defects, macrophage, cytokine and miscellaneous defects, phagocyte dysfunction, and complement deficiencies [4]. *Acquired* conditions include malnutrition; viral infection, e.g., HIV; malignancy; drugs; trauma; metabolic disorders; and environmental exposure [5]. The most frequently implicated organisms in opportunistic CNS infections in immunocompromised children may be bacterial, parasitic, fungal, or viral species.

Bacterial infections

Infection with *Mycobacterium tuberculosis* remains a condition directly associated with poverty and socio-economic disparity. Most healthy individuals do not develop active disease, while HIV-infected patients are about six times more likely to develop TB and are particularly susceptible to extrapulmonary TB [6]. Primarily a pulmonary infection, about 95% of cases are contained by cell-mediated immunity, with spread to the CNS occurring in about 1% of cases [7, 8]. Tuberculous meningitis (TBM) in immunocompromised patients demonstrates higher drug resistance and mortality rates, attributed mostly to delayed diagnosis, which is common in most developing countries [9]. TBM is the commonest and most lethal neurologic presentation, but focal parenchymal lesions such as tuberculomas or tuberculous abscesses and tuberculous osteomyelitis, either of the skull or vertebrae (Pott's disease), are also encountered. In TBM, there is a typically thick gelatinous exudate in the basal cisterns, leading to hydrocephalus and cerebrovascular inflammation and subsequent ischemia, raised intracranial pressure (ICP), and parenchymal injury [10, 11].

A positive history of TB contact with a positive tuberculin skin test or Mantoux is highly suggestive. Chest X-ray findings typical of pulmonary TB are well described, and the

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organism may be identified or cultured from sputum or gastric washings [12]. New molecular diagnostic tools like the Xpert MTB/RIF have been introduced and are being validated for CNS disease [4].

The typical imaging appearance of TBM is often described as a triad of contrast enhancement of the basal meninges with hydrocephalus and infarcts [5] (Fig. 1a, b). Hypodensities related to cerebral ischemia are common in the so-called TB zone, the vascular territory of the middle cerebral artery, involving the lenticulostriate and thalamoperforating vessels [8, 9].

Treatment with four drugs for 6 months [10] is usually advocated, with some recommending 9–12 months [13–15]. Pyridoxine should be prescribed with INH to prevent peripheral neuropathy. Follow-up imaging is of value in detecting complications such as hydrocephalus and infarcts [15]. The optimal management of tuberculous hydrocephalus (TBH) is controversial with most institutions developing their own treatment algorithms with respect to the indications for surgery and the choice of operation [16, 17]. Ventriculoperitoneal shunts (VPS) have been the most widely described option, though the reported complication rate has been high [18–20]. A selective approach of first inserting an external ventricular drain (EVD) as a temporary measure and then shunting those who responded favorably has been recommended [21, 22]. Endoscopic third ventriculostomy (ETV) in this setting has also been reported but can be technically quite challenging as the floor of the third ventricle is usually opaque and thickened with exudate and adhesions obscuring the pre-pontine cisternal space [18–20, 23] (Fig. 2). Some authors report greater success with ETV in chronic TBH when the acute exudate has resolved [16, 24, 25].

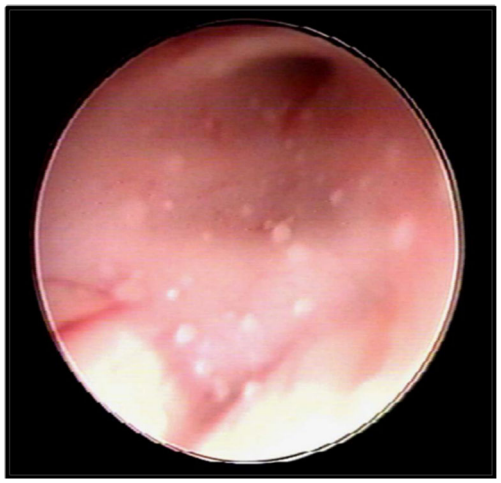

Fig. 2 Intraoperative endoscopic view of the thickened, opaque floor of the third ventricle in tuberculous meningitis

Small solitary lesions that present with seizures alone may be difficult to distinguish from cysticercal granulomas and in the absence of active tuberculosis elsewhere may not require treatment other than anticonvulsants; larger lesions should be treated with the standard four-drug regimen [8].

With appropriate antituberculous therapy, the majority of children with TBM survive, but long-term neurological and psychological outcome remains poor [13, 26].

Parasitic infestations

Parasitic infestation of the central nervous system affects millions of people, mostly in the developing world where poverty

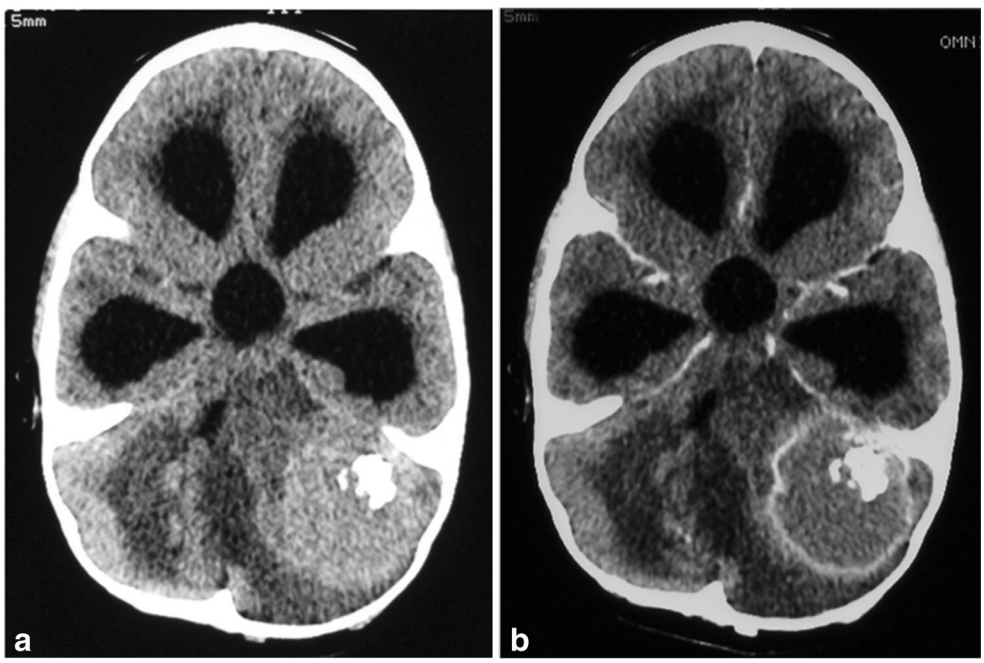

Fig. 1 CT scan demonstrating a posterior fossa tuberculoma with compression of the fourth ventricle and associated obstructive hydrocephalus, (**a**) pre-contrast and (**b**) post-contrast

and related conditions prevail, although a change in the geographic distribution of these diseases has become more evident in the era of globalization [8].

Parasitic infestations can be broadly classified as *protozoan* (single-celled organisms) and *metazoan/helminthic* (complex, multicellular organisms).

Toxoplasma gondii is an obligate intracellular protozoan parasite with a worldwide distribution, first identified in the human retina [27, 28]. The increasing number of immunocompromised patients, either due to HIV infection or immunosuppression, has led to the emergence of toxoplasmosis as a potentially life-threatening opportunistic infection [29, 30].

In CNS infection, the cerebral gray matter is diffusely involved, resulting in meningoencephalitis and foci of perivascular inflammation, with basal ganglia and periventricular calcification reported in the fetus [31, 32]. In immunocompromised hosts, widespread necrotizing lesions may occur within the CNS and other organs [33]. In congenital toxoplasmosis, hydrocephalus may result from obstruction at the foramen of Monro or aqueduct of Sylvius. The disease in children occurs in three categories: congenital, postnatally acquired, and ocular.

Congenital toxoplasmosis is often subclinical but may present with fever, hydrocephalus, chorioretinitis, cerebral calcification, seizures, microcephaly, and an abnormal CSF (markedly raised protein and mononuclear pleocytosis) or systemic involvement such as hepatosplenomegaly and jaundice [34, 35]. The severity of the clinical disease in congenitally infected infants is inversely related to the gestational age at the time of maternal infection [29] and must be differentiated from other perinatal encephalopathies cause by cytomegalovirus, herpes simplex virus, rubella virus, and certain metabolic and storage diseases [36].

The diagnosis of congenital toxoplasmosis can be made through a combination of clinical examination, radiological features, CSF, and serological analysis, as well isolation of *T. gondii* from tissue or fluid specimens in acute infection [37, 38]. Repeat fetal ultrasound may demonstrate rapidly progressive, symmetrical ventricular dilatation as the most common finding. When fetal toxoplasmosis infection is confirmed, antibiotic treatment with sulfadiazine and pyrimethamine together with folinic acid has been recommended [36, 39], with prednisone if CSF protein is elevated or sight-threatening chorioretinitis occurs [36]. Untreated congenital toxoplasmosis has a poor prognosis, with prolonged treatment substantially improving the frequency and severity of neurological sequelae [40, 41]. Toxoplasmosis and coexistent HIV infection in children are rarer than in adults [42], especially since the advent of highly active antiretroviral therapy (HAART).

Hydrocephalus may be associated with congenital toxoplasmosis due to either obstruction at the outlet foramina and aqueduct of Sylvius as well as impaired absorption at the arachnoid villi [43, 44]. The nature of the hydrocephalus, i.e., obstructive or non-obstructive, has important implications regarding the treatment options.

Acquired toxoplasmosis remains asymptomatic in most cases. With CNS involvement, the predominant symptoms are headache, disorientation, and drowsiness, and it should be considered in the differential diagnosis whenever evidence of acute CNS disease occurs in immunocompromised patients [36].

Toxoplasmosis of the central nervous system occurs in up to 40% of all HIV infected patients and is the most common opportunistic infection to cause focal brain lesions [45, 46]. While often asymptomatic in children and adults, three different neurological patterns are evident in toxoplasmosis of the CNS, diffuse encephalitis with or without seizures, meningoencephalitis, and single or multiple mass lesions [47].

The diagnosis of toxoplasmosis of the CNS is made on history of exposure and risk factors, clinical examination, serological/CSF testing (where LP is safe), and radiological features. On radiological imaging, cerebral toxoplasmosis often appears as multiple lesions (> 5 lesions), demonstrates ring enhancement with contrast, is typically located in the basal ganglia or the gray-white matter interface, has minimal mass effect with mild edema, and often has evidence of cerebral atrophy [14]. Pyrimethamine, sulfadiazine, and folinic acid are used with surgical intervention reserved for diagnostic biopsy in cases where the diagnosis is unclear or for relief of mass effect. The prognosis of toxoplasmosis involving the CNS, particularly in those who are immunocompromised, is poor [48–50]. Early diagnosis and aggressive treatment are essential to obtain the best outcome. Prevention is fundamental in reducing both congenital and acquired toxoplasmosis. Recommendations include avoiding contact with cat litter, cooking meat to higher than 150 °F, washing fruit and vegetables thoroughly, and cleaning cooking surfaces carefully.

Neurocysticercosis, caused by the larval stage of the helminthic tapeworm *Taenia solium*, is the most common CNS parasitic infestation in humans and the commonest cause of acquired epilepsy [51, 52]. Cysticercosis is widely endemic in the developing world where pork is consumed and sanitation is poor, especially in Central and South America, non-Islamic regions of Asia and sub-Saharan Africa [53]. In certain developed countries, the prevalence may be influenced by the increasing migrant workforce [53–61]. The life cycle of *T. solium* involves humans as definitive hosts and pigs as intermediate hosts. The cycle is completed when a human inadvertently consumes *measly* pork, contaminated with viable *T. solium* eggs, which enter the mucosa of the small intestine, mature and then spread hematogenously to the muscle, brain, and skin [62, 63]. Once it enters the brain parenchyma, development occurs through four identifiable phases: *vesicular phase*—viable cyst with minimal host response; *colloidal phase*—degenerating cyst ruptures into surrounding

parenchyma and incites a strong immune response; *granular-nodular phase*—further degeneration, forming a nodular cyst; and *calcified phase*—cyst dies and calcifies [64].

Immunocompromised patients appear more susceptible to multiorgan involvement, with HIV coinfection in neurocysticercosis increasing the risk of basilar meningitis and the formation of giant cysts [65, 66]. A useful classification for neurocysticercosis is based on viability and location: *active*—parasite is alive, *transitional*—degenerating parasite, and *inactive*—parasite is dead [64]. Each of these can be subclassified into parenchymal and extraparenchymal, i.e., meningeal, intraventricular, and subarachnoid forms [50, 62]. *Cysticercus cellulosae* is used to describe thin walled 3–20 mm sized cysts within the parenchyma, and *Cysticercus racemosus* refers to larger, "grape-like" vesicles mostly located in the subarachnoid cisterns, ventricles, or sylvian fissure [63, 67]. Clinically manifestation of neurocysticercosis depends on the size, number, location, and developmental stage of the cysticerci and also the host immune response [63]. *Parenchymal lesions* present with seizures or focal neurological deficits caused by direct compression. Cranial nerve palsies may be caused by vasculitis or fibrous adhesions. *Intraventricular or cisternal lesions* usually present with raised intracranial pressure and hydrocephalus resulting from obstruction of CSF flow due to widespread arachnoiditis and adhesions [68]. Other neurological sequelae include neurocognitive impairment, altered mental state, brainstem dysfunction, stroke-like symptoms, and extrapyramidal signs [69]. Proposed diagnostic criteria have been based on objective clinical, imaging, immunological, and epidemiological data [65]. In a hospital setting, neuroimaging remains the mainstay, with definitive diagnosis made on the basis of histopathologic evidence.

Lateral X-rays of the thigh and calf may demonstrate cigar-shaped calcifications. CT scans during the active phase of the disease reveal single or multiple hypodense lesions of varying sizes with a hyperdense mural nodule (Fig. 3). Ring enhancement suggests perilesional inflammation, and calcification denoting inactive lesions may be present in about 50% of cases. MRI is more reliable in demonstrating smaller cysts in the ventricles and subarachnoid spaces, with distinctive features on both T1- and T2-weighted imaging [66].

CSF mononuclear pleocytosis with raised protein and decreased glucose is typical with extraparenchymal disease [70]. Enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunoelectrotransfer blot (EITB) are the most widely used immunodiagnostic methods for diagnosing human cysticercosis [71]. In children with a single intracerebral lesion, EITB can yield false-negative results in 75% of cases; serological results, therefore, need to be interpreted together with clinical and radiological findings [72].

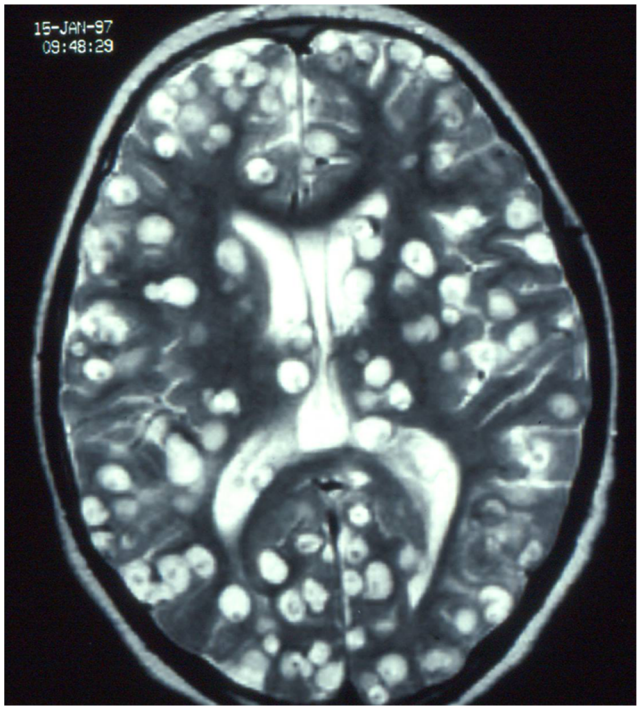

Fig. 3 Multiple active intracranial parenchymal neurocysticercal lesions

Treatment for neurocysticercosis includes antiparasitic agents, symptomatic medication, and surgery. Antihelminthic drugs praziquantel and albendazole are generally considered as part of long-term seizure control and for persisting/enlarging parenchymal lesions. They should be used with caution in cases of raised ICP, as the inflammatory response they evoke could precipitate further neurologic deterioration [73]. Albendazole is preferred over praziquantel, which has a lower efficacy on extraparenchymal lesions, interacts with steroids and antiepileptics, and may increase the risk of stroke [74–76]. Corticosteroids together with antihelminthics are recommended to reduce the inflammatory reaction induced by death of the larvae. First-line antiepileptic drugs remain the primary therapy for seizure control in neurocysticercosis [73], with gradual reduction in the medication after resolution on imaging studies recommended [52–54]. Standard treatment regimens appear effective in immunocompromised patients as well; however, the impact of antiretroviral therapy and immune reconstitution remains uncertain [77].

Neurosurgical interventions are required for confirming tissue diagnosis, relieving mass effect, and treating raised ICP and CSF diversion for hydrocephalus. Hydrocephalus may require insertion of an EVD as a temporizing measure. VPS failure rates in neurocysticercosis are reported as high as 67% [78]. Endoscopic approaches have gained increasing popularity for removing ventricular neurocysts and treating hydrocephalus [79–81]. The eradication of cysticercosis is dependent on improvement of human sanitation and public health infrastructure.

Amebic encephalitis in humans was first reported in 1965 [82]. Free-living amoebae thrive in warm water environments, and those causing CNS infection include *Balamuthia mandrillaris*, *Entameba histolytica*, and *Naegleria fowleri*. While amoebic encephalitis is rare, it is unfortunately almost always fatal. *N. fowleri* usually leads to primary amebic meningoencephalitis (PAM), while the other amoebae usually lead to granulomatous amebic encephalitis (GAE). PAM typically presents with fever, severe headache, and symptoms of raised ICP within a fortnight of exposure to contaminated water. GAE usually has a more protracted course, lasting weeks to months, often as an opportunistic infection in immunocompromised, HIV-infected patients [83]. The symptoms are initially non-specific, progressing to altered mental status and focal neurological deficit, eventually proving fatal within several weeks. Diagnosis depends on a focused history, asking for recent exposure to stagnant water bodies, clinical examination, imaging features, and identification of the organism on wet smear [24, 84]. Treatment should be aggressive and include antimicrobials such as, amphotericin B and metronidazole. Steroids and osmolar therapy should be considered for raised ICP. Surgery may be necessary in cases with space-occupying lesions and raised ICP.

Cerebral malaria, although not routinely considered an opportunistic infection, immunosuppression may have a negative impact on its natural history [85]. Even with treatment and supportive care, cerebral malaria has a reported mortality rate of 20–50%, with most reported fatalities occurring in African children [24, 86]. Fever is the clinical hallmark of cerebral malaria, while other diagnostic features include coma, seizures, identification of *Plasmodium falciparum* or *Plasmodium vivax* on blood smear, and exclusion of other causes of encephalopathy [87]. Management includes adequate resuscitation, supportive care, and commencement of antimalarial treatment, the details of which fall outside the scope of this article.

Fungal infections

Fungal invasion of the CNS generally results in subacute or chronic meningitis, encephalitis, parenchymal brain abscesses/granulomas, or vasculitis [88]. The diagnosis is usually made in a vulnerable patient with a history of exposure, confirmed by serological tests, CSF analysis or histopathological examination. Treatment usually requires long-term antifungal medication and CSF diversion in patients who develop hydrocephalus. Some of the more common CNS fungal infections are briefly discussed below [89].

Cryptococcosis—CNS infection with *Cryptococcus neoformans* species—remains one of the most common opportunistic infections in immunocompromised patients [90]. The clinical presentation is typical of meningitis, with severe, often unbearable headache, malaise, with or without fever [88] and usually follows a subacute or chronic course with features of raised ICP. Laboratory diagnosis is usually made using India ink stain or serological testing (Cryptococcal latex antigen test—CLAT). Recommended treatment differs in HIV infection, but generally includes amphotericin B with flucytosine (for 2 weeks), followed by oral fluconazole for 8 weeks. Raised ICP can be managed with serial lumbar punctures, though a lumboperitoneal shunt may be required in patients who develop hydrocephalus [16, 91].

CNS aspergillosis is usually caused by the organism *Aspergillus fumigatus*. Infection most commonly presents as an abscess and less commonly as meningitis (Fig. 4a, b). Excision of these lesions is recommended, as they may cause vascular invasion and can lead to the formation of mycotic aneurysms. Combination therapy with antifungal drugs and surgery has improved outcome [92].

Histoplasmosis is a systemic mycosis acquired via the respiratory system. CNS involvement may be a manifestation of disseminated disease or may be an isolated illness [93]. Neurologic syndromes include subacute or chronic meningitis

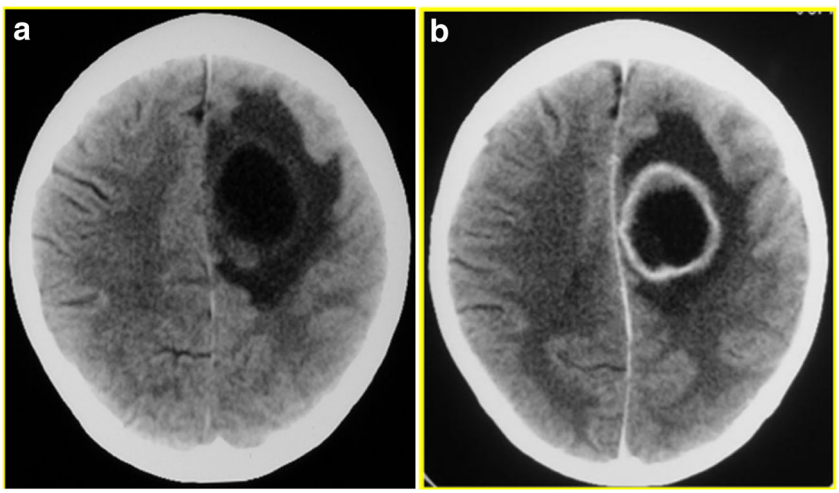

Fig. 4 **a**, **b** CT scan demonstrating left parietal *Aspergillus* brain abscess, pre- and post contrast

and focal lesions (histoplasmosis). Positive diagnosis requires CSF (at least 10 ml), meningeal, or brain tissue [93]. Optimal treatment for CNS histoplasmosis is presently unclear, but amphotericin B and fluconazole are the main options.

In Coccidioidomycosis, CNS infection with the dimorphic fungus *Coccidioides immitis*, mostly seen in immunocompromised patients, leads to basal meningitis, often with hydrocephalus.

Early shunt placement is often required, together with antifungal therapy [94].

Sporotrichosis very rarely involves the CNS, but cases of meningitis have been described in HIV-infected patients. Imaging usually reveals non-enhancing lesions in the brainstem, basal ganglia, thalamus, and centrum semiovale, with meningeal enhancement [95]. Amphotericin B remains the treatment option for meningitis.

Candida species, while less virulent than *Aspergillus*, are the most common pathogen in patients with end-stage HIV. They often colonize central lines, external ventricular drains, and shunts. They can, therefore, either complicate the treatment of underlying hydrocephalus or be the causative organism [96]. Prevention of fungal colonization and control of local disease are important as prior colonization with *Candida* is a major risk factor to developing systemic candidiasis [97].

Viral infections

Cytomegalovirus (CMV) is acquired early in life and usually remains in latent state. In immunocompromised patients, primary infection with CMV can cause significant morbidity [98, 99]. The predominant presentation with CMV in immunocompromised patients is retinitis, and funduscopic examination usually confirms the diagnosis. Antiviral agents have been used for prophylaxis and treatment of CMV.

While other viral infections caused by Herpes simplex 2 (HSV2), Epstein-Barr virus, and JC virus (progressive multifocal leukoencephalopathy—PML) have been described, they very rarely cause CNS infection in children and have been included for completeness only.

Conclusion

The management of CNS infection in the immunocompromised child remains a challenge to most pediatric neurosurgeons. An awareness of the most common pathogens and the treatment modalities peculiar to these infections remains fundamental to optimal management.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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