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Cytomegalovirus (CMV) Encephalitis in HIV Patients

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Mini Review

In HIV patients with low CD4 count, CMV is a significant cause of morbidity and mortality.

It is hypothesized that impaired CD4 cell functioning is attributable to viral replication. Most cases of CMV encephalitis occur when CD4 counts fall below 50, however patients may be predisposed to CMV infection prior to depletion of CD4 [1]. Previous opportunistic infections (OIs), a high level of CMV viremia, and high plasma HIV RNA levels (>100,000 copies/mL) are other reported risk factors [2].

Many studies have reported that the incidence of CNS infections in HIV patients has decreased and mortality has improved since the introduction of ART [3-7]. Neunberg et al reports a decreased in rate of CMV encephalitis from 21.9% before 1987, to 9.5% after the introduction of ART [6]. With antiretroviral therapy (ART), the median survival of patients with CMV encephalitis has improved by 3 months.

CMV encephalitis can also be characterized by: focal parenchymal necrosis, ventriculo-encephalitis with focal or diffuse destruction of ependymal lining and periventricular tissue [8]. Given the lack of typical clinical features in most of cases, clinical diagnosis of CMV encephalitis has been made in less than 2% of the patients, but 10% to 14% of the patients have been found to have CMV encephalitis on autopsy [9].

Clinical Features of CMV Encephalitis

CMV neuroinvasive disease in HIV manifests as retinitis, encephalitis or radiculomyelitis [10]. Autopsy studies have shown CMV retinitis in 32% [11], encephalitis in up to 30%, but polyradiculomyelitis occurred in only 2% of patients with AIDS and neurological disease [12]. Diffuse encephalitis is the most common form and presents as dementia with neurologic symptoms of reduced memory, attention, and concentration although cranial nerve deficits, ataxia, hemiparesis and hemianopsia are also reported [13-15]. Often the presentation can be difficult to differentiate from HIV associated encephalopathy [16].

Ventriculoencephalitis is a more rapidly progressively form, often characterized by focal neurological signs, cranial nerve deficits and nystagmus, and lesser neuropsychological symptoms [2]. However, it may be very difficult to distinguish between ventriculoencephalitis and diffuse encephalitis solely on the basis of clinical features [13].

CMV myelitis is a form of necrotizing myelitis resulting in paraplegia or tetraplegia [10], whereas poyradiculo-myeloptahy manifests with ascending are flexia, hypotonic paresis, paresthesia's and early urinary retention [17-19].

Diagnosis

There are multiple modalities that can be utilized for the diagnosis of CMV encephalitis in HIV patients. One of the most sensitive and specific tests for diagnosis is analysis of the viral DNA and detection of pp65 in polymorphonuclear leukocytes of the CSF by PCR [20]. CMV infection will usually present with negative bacterial cultures and an increase in CSF WBC's that are predominantly neutrophils [21]. Studies have shown that imaging modalities are not highly sensitive for the detection of CMV encephalitis in HIV patients, however, periventricular inflammation and/or ventricular enhancement with or without ventriculomegaly are supportive findings [22]. In some confirmed cases, cortical atrophy and diffuse white matter hyperintensity on MRI has been reported [23]. CMV infected patients can also present with evidence of retinitis with fundoscopy demonstrating hemorrhagic infarction and retinal opacification [2].

Treatment

For HIV patients who develop CMV encephalitis, the recommended treatment regimen is combination IV therapy with ganciclovir 5 mg/kg every 12 hours and foscarnet 60 mg/kg every 8 hours (an alternative dosing to consider is 90 mg/kg every 12 hours) [2]. The recommendation for dual treatment is based on the high mortality rates seen in patients with CMV-related neurological disease [24-27]. Randomized controlled trials are lacking, so evidence primarily consists of case reports and extrapolation of data from CMV retinitis treatment. The available evidence indicates that treatment with ganciclovir and foscarnet together results in better outcomes than when either agent is used alone [24-29]. However, there is no established duration of treatment or recommendation for transition to maintenance therapy, so practice is generally influenced by trials of CMV retinitis or relapsed retinitis [6-8]. Induction therapy with both ganciclovir and foscarnet is at least 14 to 21 days but may be extended depending on clinical status and CSF studies [2,24,25]. Maintenance therapy may include lower doses of ganciclovir/foscarnet combination therapy, ganciclovir or foscarnet monotherapy, or valganciclovir monotherapy at 900 mg orally daily [24-25]. Treatment should be continued until the CD4 count is greater than 100 cells/mm^3 for at least 6 months [2,24]. Ganciclovir is associated with neutropenia and thrombocytopenia, while foscarnet may cause renal toxicity [30]. These adverse effects can be dose limiting and require monitoring, especially with long durations of treatment [30].

Drug Resistant CMV

Drug-resistant isolates of CMV were first reported in 1989, but incidence has been reported as decreasing (28% resistance prior to 1996 and 9% since 1996) with the availability of effective ART in HIV/AIDS patients [31,32]. The decline in reported resistance has been

attributed to better control of CMV replication with ART. Resistance-associated mutations have been identified in the UL97 kinase gene and the UL54 DNA polymerase gene [31-36]. Resistance is characterized by an increase in drug concentration required to reduce the viral growth by 50% [33,34]. Viral UL97 kinase gene mutations confer ganciclovir resistance, but viral UL54 DNA polymerase gene mutations can confer resistance to any of the standard anti-CMV antiviral agents (ganciclovir, foscarnet, and cidofovir) [34,35]. Resistance is unusual in the first six weeks of therapy, but should be suspected when persistent or increasing CMV viral loads are reported or progression of disease occurs after several weeks of appropriate anti-CMV therapy [33,36-38]. Treatment options are limited in this patient population, usually resulting in combination therapy with multiple antiviral agents – most commonly ganciclovir plus foscarnet [36]. If any UL97 mutation is present, foscarnet therapy is normally indicated. For UL97 mutations that result in low-grade resistance of ganciclovir, it may be possible to double the standard induction dose of ganciclovir to overcome resistance in clinically stable patients [39]. Cidofovir can also be considered in patients where ganciclovir resistance is only due to a UL97 mutation [33]. In patients with a UL54 mutation, high grade foscarnet resistance is rare but may confer low-grade ganciclovir with or without cidofovir cross resistance [34,40]. In patients with confirmed resistance to all standard anti-CMV or in those who are not clinically improving, other agents that have been used in the transplant population include: artesunate, maribavir, and leflunomide [41-43].

Conclusion

HIV patients who present with neurologic symptoms of reduced memory, attention, and concentration or sudden onset of mental status change high on the differential diagnosis should be CMV encephalitis. Early aggressive treatment with dual antiviral agents suggests better outcomes for the patients. Seek infectious disease /HIV specialist's expertise if available.

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