Human Immunodeficiency Virus (HIV)-Associated CD8 Encephalitis

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Overview

It is estimated that over 35 million people worldwide are infected by the human immunodeficiency virus (HIV), with nearly two million new infections each year [1]. Despite a modest 10% decrease in the incidence of new HIV infections in the United States (USA) in recent years, the prevalence of HIV continues to rise in conjunction with better survival rates. An estimated 1.1 million people in the USA are currently living with HIV disease [2]. HIV is primarily transmitted by way of unprotected sexual contact with men, as well as by injection drug use: In the USA, HIV transmission rates are highest among men who have sex with men, particularly for young racial and ethnic minorities [3]. The life expectancy for HIV-infected persons in the USA has almost normalized due to the widespread use of effective combination antiretroviral therapy (cART), beginning in the mid-1990s [4]. Nevertheless, HIV persists as a serious public health problem, as there are significant gaps in its detection and treatment across the continuum of care in the USA and worldwide [5]. At the population level, HIV suppression rates remain well below clinical targets, and the disease is associated with elevated rates of mortality and morbidity, including central nervous system (CNS) complications.

This chapter specifically reviews the available research on one such CNS complication of HIV disease: CD8 encephalitis. This chapter begins by providing a historical context for HIV-associated CD8 encephalitis (HIV-CD8E), which is one of the many CNS complications of HIV disease that have evolved in step with the development and widespread availability of effective cART. Next, this chapter briefly

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outlines the current epidemiology, pathogenesis, and clinical presentation of HIV-associated CNS complications in the era of cART, including immune reconstitution inflammatory syndrome (IRIS). This chapter then provides an in-depth review of the available scientific evidence for HIV-CD8E, which derives from an emerging literature that is almost exclusively based on case studies and series. As such, this chapter attempts to meaningfully stitch together the available threads of evidence regarding the clinical presentation, diagnosis, management, course, and pathophysiology of HIV-CD8E. This chapter concludes by highlighting gaps in the current science and clinical management of HIV-CD8E, which may guide future research efforts.

Historical Context of HIV-Associated CNS Complications

In 1981, a case series from the Centers for Disease Control [6] reported an unusual incidence of cancer (i.e., Kaposi's sarcoma) and opportunistic infections (i.e., Pneumocystis pneumonia) in New York and California among men who had sex with men (MSM). The causal agent for this emergent acquired immunodeficiency syndrome (AIDS) was identified in 1983 as a T-lymphotropic retrovirus [7], which is believed to have evolved from a simian immunodeficiency virus (SIV) that adapted to human hosts in sub-Saharan Africa during the early part of the twentieth century [8]. Clinical reports of CNS symptoms accompanying HIV infection emerged early in the course of the AIDS epidemic in the USA: that is, a subset of affected patients was showing "organic" mental and neurological symptoms [9]. In 1983, Snyder et al. [9] reported the first systematic case series of AIDS-related CNS complications, including frank dementia, which was sometimes the initial manifestation of illness and was often a harbinger of imminent mortality. Whether these striking neurobehavioral syndromes stemmed from the direct CNS effects of HIV infection itself and/or secondary to CNS opportunistic infections was controversial. Indeed, CNS tumors (e.g., lymphoma) and opportunistic infections were quite common in the pre-cART era [10] and included fungal (e.g., cryptococcal meningitis), viral (e.g., encephalitis due to *progressive multifocal leukoencephalopathy* or cytomegalovirus), and parasitic (e.g., toxoplasmic encephalitis) agents. Nevertheless, HIV itself was also associated with a specific neuropathological finding, namely, fused microglia and perivascular macrophages that formed the multinucleated giant cells (aka syncytia) that are now characteristic of HIV encephalitis. Further support for HIV's direct contribution to CNS symptoms arose from studies showing that milder forms of neurobehavioral disturbance (e.g., apathy, neurocognitive impairment) were evident in the absence of CNS opportunistic infections and in otherwise asymptomatic HIV-infected patients [11].

HIV-Associated CNS Complications in the Era of cART

The widespread use of effective cART in the modern era has drastically altered the neurological landscape of HIV disease in developed countries. The incidence and prevalence of frank HIV-associated dementia is currently well below 5% [12], and CNS opportunistic infections are the exception rather than the norm. Nevertheless,

the prevalence of CNS complications, including HIV-associated neurocognitive disorders (HAND) remains high and can often represent a serious challenge to clinicians and researchers. In practical terms, a diagnosis of HAND means that an individual shows evidence of impairment (i.e., a significant decline from estimated premorbid levels) in two or more cognitive domains (e.g., attention, executive functions, memory, processing speed, and motor skills) that is at least partly explained by HIV disease [13]. In the modern era, it is estimated that 30–50% of HIV-infected persons meet criteria for HAND. Incidence rates vary between 5% and 20% [14], and the course of HAND is highly variable; that is, unlike many neurodegenerative conditions, HAND is not associated with inevitable progression to dementia and death. In 30–60% of cases, the impairment associated with HAND is mild to moderate and at least partly interferes with daily activities, leading to a diagnosis of HIV-associated minor neurocognitive disorder (MND). In 30–60% of cases, the impairment is mild to moderate and does not interfere with daily activities, which is termed HIV-associated asymptomatic neurocognitive impairment (ANI). In less than 5% of cases, the impairment is severe and markedly interferes with daily activities, thus warranting a diagnosis of HIV-associated dementia (HAD). Of course, these epidemiological estimates vary depending on the criteria [15] and specific diagnostic methods [16].

The neuropathophysiology of HAND remains poorly understood in the cART era, and there are no well-validated diagnostic biomarkers or effective treatments. That said, current models propose that HIV is indeed neurovirulent and crosses the blood-brain barrier early in the course of infection, imbedded in activated monocytes and other white blood cells that traffic into brain parenchyma [17]. HIV does not widely *infect* neurons, but it does carry direct and indirect adverse CNS effects on brain structure and function. In terms of its direct effects, HIV is detectable in brain parenchyma and can replicate in perivascular macrophages, astrocytes, and microglia, which may express neurotoxic viral proteins like gp120 and Tat [18]. HIV's indirect effects on the brain are primarily from neuroinflammatory processes, such as upregulation of cytokines and chemokines that can alter neuronal functioning [19]. Well over half of HIV-infected persons will evidence some form of neuropathology upon autopsy [20]. Unlike the pre-cART era in which HIV-E and CNS opportunistic infections were most prevalent, HIV-associated pathologies in the cART era are quite heterogeneous and include neural apoptosis, synaptodendritic injury, encephalitis, gliosis, and vasculopathy [18]. Such pathological diversity has made the quest for discovering a biomarker of HAND quite challenging. A host of different plasma and CSF biomarkers reflecting these neuropathogenic processes have been examined in the context of HAND, including markers of chemokines (e.g., MCP-1), astrocytosis (e.g., S-100β), neuroinflammation (e.g., tumor necrosis factor-alpha), and neuronal damage (e.g., neurofilament light) [19], with varying levels of success. Similarly, although the prevalence and severity of HAND can increase with the clinical severity of immunovirological disease, this relationship is generally quite weak and nonlinear in the cART era [12]. Nadir (i.e., lowest) $CD4^+$ cell count shows modest correspondence to the level of neurocognitive impairment in the cART era (e.g., [21]), but the value of that historical immune marker may dwindle under evolving cART guidelines in which patients are treated despite high CD4 counts.

Although the effects of HIV can be observed throughout the brain, HIV-associated neural abnormalities are most commonly present in the white and gray matter structures of fronto-striato-thalamo-cortical circuits [22]. Accordingly, the neurobehavioral profile of HAND parallels that which is observed in other primarily frontal systems conditions, such as Parkinson's disease; specifically, HAND is often marked by mild-to-moderate deficits in executive functions, working memory, psychomotor speed/coordination, and the strategic aspects of learning and memory, with relative sparing of memory consolidation (i.e., amnesia is uncommon), visuospatial abilities, and praxis. In recent years, investigators have begun to raise the possibility that as the HIV population ages, HAND is evolving into a more posterior cortical disease, akin to Alzheimer's disease; however, neurobehavioral evidence for such claim is presently scant (e.g., [23]). Effective disease modifying therapies for HAND do not yet exist. The initiation of cART is not strongly neuroprotective or restorative [24], even with regimens that penetrate the CNS [25]. Studies evaluating various nonantiretroviral agents (e.g., selegiline; [26]) and rehabilitation approaches (e.g., [27]) have generally not demonstrated widespread effectiveness in improving or restoring neurocognitive functions in HIV, although a few investigations demonstrate promising early findings [28, 29] that await confirmation in randomized controlled trials.

CNS Immune Reconstitution Inflammatory Syndrome (IRIS)

The incidence and prevalence of CNS opportunistic infections has declined considerably in the cART era [30]. At present, CNS opportunistic infections are estimated to occur in only about 1% of the HIV^+ population, particularly in the setting of immune compromise [31]. The most commonly encountered CNS opportunistic infections in the modern era include progressive multifocal leukoencephalopathy (PML) due primarily to John Cunningham (JC) virus, cerebral toxoplasmosis, and cryptococcal meningitis, as well as tuberculosis and cytomegalovirus. Opportunistic infections such as PML and cryptococcal meningitis play a key role in the immune reconstitution inflammatory syndrome (IRIS), which is a pathological inflammatory response that can occur in a variety of organ systems, including the CNS. IRIS is a clinical syndrome in which an unexpected, excessive pro-inflammatory response to a pathogen (usually an opportunistic infection) occurs within weeks or months of ART. The inflammatory response is characterized by a wide range of focal and systemic symptoms that if untreated can lead to death [32]. IRIS is commonly classified as either (1) "paradoxical," meaning that the CNS opportunistic infection is known and treated with some success prior to initiation of ART, after which clinical deterioration occurs secondary to the pathological inflammatory response, or (2) "unmasked," meaning that the diagnosis of the CNS opportunistic infection comes after the initiation of ART, which sparked the clinical deterioration [32]. The general incidence of IRIS is approximately 10% in the USA [32], with risk factors including treatment naïve, immunosuppression, and viremia, as well as some characteristics of the opportunistic infection itself. IRIS is less common in the CNS than

it is in other bodily systems and is estimated to occur in only 0.05–2% of HIV$^+$ patients. Of course, the incidence of IRIS is much higher among those persons with CNS opportunistic infections; for example, estimates of IRIS incidence are 15–20% among those cryptococcal meningitis and PML who initiate cART [33] for whom the mortality rates are estimated between 5% and 15%. Treatment typically involves corticosteroids, but there are no published guidelines, and interventions are variable depending on the specific diagnosis and clinical context. The CNS pathology of IRIS involves high numbers of CD8$^+$ cells in perivascular regions, but with lower than expected rates of CD4$^+$ cells, despite the latter increasing in the periphery.

HIV-Associated CD8E

HIV-associated CD8E is an emergent, relatively rare syndrome in which otherwise well-controlled HIV$^+$ patients experience an IRIS-like pathological inflammatory response. Unlike classic CNS IRIS cases in which an opportunistic infection and rapid immunovirological recovery are typically key features of the encephalitis, CD8E cases do not have an immediately identifiable pathogen. In 2013, Lescure et al. [34] provided a detailed case series of 14 HIV$^+$ patients observed near Paris, France, between 1999 and 2008 (see also Gray et al. [35] for the neuropathological findings from 10 of these patients). The majority of Lescure's [34] patients were under good immunovirological control but nevertheless experienced severe encephalitis for which comprehensive work-ups did not yield any significant precipitant. Indeed, brain biopsies revealed only inconsistent/weak expression of HIV RNA but rather large numbers of CD8$^+$ cells in perivascular regions accompanied by activation of astrocytes and microglia. Mortality rates were high in this series, and only 30% of these patients had a positive outcome. Since then, four additional single case reports of CD8E have been published [36–39], along with one case of apparent CD8E transverse myelitis [40]. Subsequent authors (e.g., the accompanying commentary by Langford and Letendre [41]) have noted the clinical and pathological similarities between Lescure's [34] CD8E syndrome and prior case studies of CNS IRIS that were published around the same time as Lescure's patients were being followed in clinic [42–44]. As such, it appears that CD8E, while rare, is not an isolated neurological complication of HIV infection whose incidence has remained steadily low during the cART era.

So, if CD8E occurs in the absence of the typical signs of CNS IRIS and other types of HIV-associated neurological complications (e.g., leukoencephalopathy), what then are its precipitants and underlying mechanisms? Lescure et al. [34] proposed that the driving neurobiological force of CD8E is a "transient disequilibrium between HIV and brain immunity." Specifically, it is posited that peripheral T cells are re/activated and then migrate across the blood-brain barrier. Although the precise source of the re/activation is unknown (and may be multifaceted), possible triggers include HIV DNA reservoirs in the brain or other latent infections. In the published case studies to date, CD8E triggers have included minor infections, virological escape (e.g., high CSF HIV RNA levels without

viremia in plasma), CNS IRIS, and cART interruption. Low levels of HIV replication and/or HIV DNA reservoirs may play a role in the re/activation of T cells; in fact, the $CD8^+$ response to covert HIV infection in the brain has even been proposed as a primary mechanism for persistence of HAND in the cART era [41]. The $CD8^+$ cells eventually "overshoot" the original target that triggered their re/activation, now outnumbering $CD4^+$ cells in the brain [34]. $CD8^+$ cells are rare in healthy brains but can be present in gray and white matter in the setting of infection and/or encephalitis and produce direct or indirect injury to neurons, particularly when they outnumber $CD4^+$ cells [45]. In the case of CD8E, pathology shows marked-to-severe CD8 cells and microglial activation, along with marked astrocytosis and white matter changes indicative of edema and myelin loss [35]. There is a weak presence of HIV P24 and $CD4^+$ cells and no evidence of the hallmark multinucleated giant cells.

Clinical Presentation and Diagnosis

Neurological Symptoms

The presenting neurological symptoms of CD8E appear to be fairly diverse, although there are some patterns emerging. One or more of the following four neurological symptoms were evident in approximately 30–45% of CD8E cases reported to date: cognitive impairment, headache, seizures, and/or confusion. Across this small literature, it appears that men may be more likely than women to present with cognitive impairment (56% vs 13%), which includes dementia and memory difficulties. By way of contrast, women may be more likely than men to report headache (75% vs 22%). Less frequent presenting symptoms of CD8E (<15%) have included dizziness, gait abnormalities, imbalance, tremor, facial palsy, coma, or dysarthria.

Laboratory Findings

Flow cytometry reveals a high number of $CD8^+$ cells in the CSF. Protein levels are typically elevated. HIV RNA has been detectable in the CSF of 11 out 12 cases reported thus far, most often in the setting of undetectable (or sometimes much lower) HIV RNA in plasma, suggesting viral escape.

Neuroimaging

FLAIR MRI of CD8E patients tends to show bilateral, diffuse signal intensities that are nonspecific and suggestive of leukoencephalopathy [34, 35] (see Fig. 10.1). However, Lescure et al. [34] observed that postgadolinium contrast (spin-echo T1 with magnetization transfer) revealed a highly sensitive and specific pattern of "multiple punctate or linear gadolinium-enhanced lesions" in the perivascular region. In four patients, these image lesions were confirmed with high-intensity signal on diffusion-weighted scans (see also [39]). The MRI findings in CD8E are usually diffuse but can be focal in their presentation in some instances (see [36]). Interestingly, the case described by Morioka was negative on T1 postgadolinium contrast but nevertheless had positive findings for CD8E on brain biopsy.

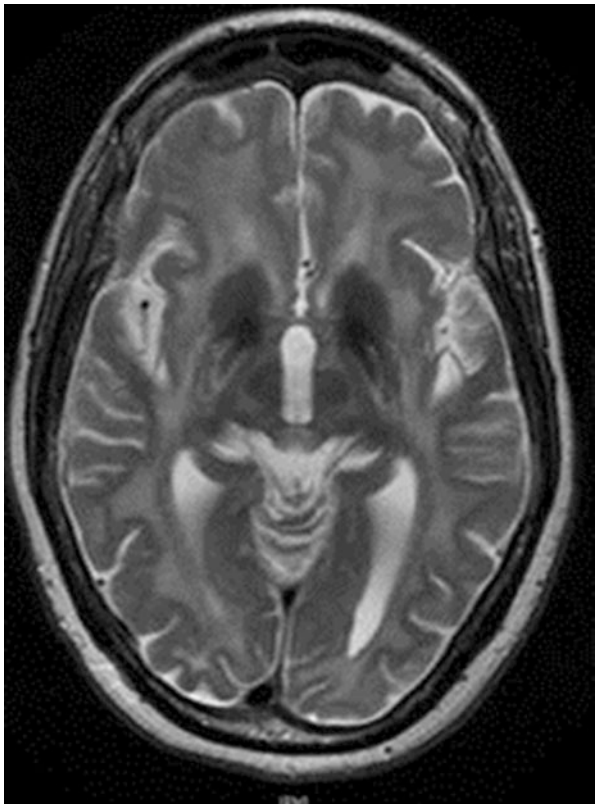

Fig. 10.1 MRI of the brain of a patient with biopsy-proven CD8 encephalitis showing bilateral white matter abnormalities

Management

Overall, the prognosis for CD8E patients is poor, but early diagnosis and prompt management are key to increase the likelihood of a positive outcome. Lescure et al. [34] suggest that the clinical features, CSF studies, and MRI (with gadolinium contrast) are sufficient to make a reliable diagnosis of CD8E without a brain biopsy. However, it should be noted that flow cytometry and gadolinium contrast scans are not always available [41]. Timely administration of combination of ART and corticosteroids shows some evidence of effectiveness across the published case studies. In the Lescure cases [34], the authors followed the recommended glucocorticosteroid treatment protocol recommended for patients with acute disseminating encephalomyelitis (ADEM). In those cases, treatment involved intravenous methylprednisolone (1 g/day for 5 days, then tapered for a median of 6 months). Salam et al. [38] detail an instance in which initial treatment with corticosteroids was effective but met with a relapse, which ultimately responded to mycophenolate mofetil. Also of note, the patient described in the Morioka et al. [37] study had a positive response to a switch in cART (i.e., without corticosteroids), which was initiated following the detection of a drug-resistant mutation (M184V).

Future Directions

As is true of many rare conditions, there is much left to learn about the epidemiology, mechanisms, clinical course, and management of CD8E. The case studies reviewed above provide important initial insights and allow for hypothesis generation, but well-designed studies with larger sample sizes and proper comparison groups are needed. For example, what are the predictors of incident CD8E (e.g., why do some minor infections trigger CD8E while others do not and what explains individual patient differences in that regard?)? What are the host and viral genetics of CD8E (e.g., why is such a large proportion of the cases in the literature thus far observed in persons of African descent?). Can CD8E be reliably distinguished from other HIV-associated neurological complications, such as CNS IRIS? What are the most robust clinicopathological correlates in CD8E (e.g., do gadolinium MRI abnormalities reliably map onto $CD8^+$ cells in the CSF and in brain biopsies?)? What is the profile and neurocognitive trajectory of CD8E? Nearly 50% of patients present with neurocognitive impairment (e.g., memory problems) and approximately 50% of those who recovered from CD8E had residual neurocognitive complications. Further downstream, among those who survive and recover, what is the impact of CD8E on daily activities and quality of life?

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