Severe HIV-Associated CD8\(^+\) T-Cell Encephalitis: Is It the Tip of the Iceberg?

Dianne Langford\(^1\) and Scott Letendre\(^2\)

\(^1\)Department of Neuroscience, Temple University School of Medicine, Philadelphia, Pennsylvania; and \(^2\)Department of Medicine, University of California, San Diego

(See the HIV/AIDS Major Article by Lescure et al on pages 101–8.)

Immune reconstitution inflammatory syndrome (IRIS) is typically thought to affect the central nervous system (CNS) only in the presence of opportunistic pathogens, such as Cryptococcus neoformans or JC virus. Immune recovery may also adversely affect the CNS in the absence of opportunistic pathogens, an idea supported by cases presented in this issue of Clinical Infectious Diseases. The report by Lescure et al describes a series of patients with human immunodeficiency virus (HIV)/AIDS who had encephalitis that was initially classified as encephalitis of undetermined origin. Upon further review, they identified massive infiltration of CD8\(^+\) T cells into the brain and propose this as a new form of “severe but treatable . . . HIV-related encephalitis” [1].

Similarities of these patients with those described in prior reports of CNS IRIS in the absence of non-HIV pathogens support the validity and potential importance of this condition. For instance, one prior report described 2 individuals with HIV-associated dementia (HAD) who died following antiretroviral therapy (ART) initiation despite HIV suppression in blood. At autopsy, diffuse infiltration of lymphocytes (as well as macrophages) was observed in white and gray matter and in the perivascular space [2]. Another report of 7 patients, 5 of whom had HAD, documented severe neuropathological changes and perivascular inflammatory cells [3]. A third report of a patient with HAD noted progression of neurocognitive disease and white matter abnormalities on imaging over a year following ART initiation [4]. Brain biopsy from this patient revealed perivascular and parenchymal infiltrates that were composed predominantly of CD8\(^+\) T cells, some of which surrounded neurons. Together, these reports support that ART-induced immune recovery can injure the brain in the absence of non-HIV pathogens. Individuals who have more severe CNS disease at the time of ART initiation may be particularly at risk.

Current and past reports also have important differences from the cases described by Lescure et al. For instance, we previously reported high levels of HIV RNA in brain tissue in cases with demyelinating leukoencephalopathy, whereas Lescure et al found only “inconstant or week expression of HIV protein.” Several of the Lescure et al cases did have HIV RNA levels in CSF that were disproportionately high relative to those in blood, a finding consistent with recent reports of CSF vireologic escape [5–8] but inconsistent with the observed low expression of HIV proteins in brain tissue. In some patients, elements suggestive of an acute disseminated encephalomyelitis–like process were also present. Specifically, 6 of the 14 patients had upper respiratory tract infections prior to onset of their neurological symptoms. Perhaps most important, many of the patients with CNS IRIS described in prior reports died, but 9 of the 14 patients reported by Lescure et al survived, perhaps due to the use of corticosteroids in conjunction with ART. If the combination of ART and corticosteroids was truly instrumental in the survival of these patients, then this could be the most important finding by Lescure et al for HIV clinicians.

The authors also make 2 other suggestions for clinicians. First, they recommend postcontrast T1 spin-echo with magnetic transfer to capture small (<2 mm), poorly delineated T2 hyperintensities in stable, treated HIV patients who develop neurologic decline. This recommendation is based on their finding that this imaging approach revealed punctate lesions that resolved on follow-up in surviving patients who received corticosteroid therapy. Second, the authors suggest consideration of initiating corticosteroids and foregoing brain biopsy when imaging results are consistent with CD8\(^+\) encephalitis and when flow cytometry of CSF-derived cells identifies that the proportion of CD8\(^+\) T cells is at least 65%.
Unfortunately, in the United States and many other countries, neither postcontrast T1 spin-echo with magnetic transfer nor flow cytometry of CSF-derived cells is routinely performed on patients who may fall into this category, limiting the impact of the recommendations for some clinical settings.

In another report published this month in *Brain Pathology* by the same group [9], neuropathological analyses were reported on 10 of the 14 cases described in this issue of *Clinical Infectious Diseases*, although the cases from the 2 reports cannot be reliably matched based on the data provided from each report. Immunolabeling of the T-cell infiltrates in brain biopsy samples from 2 cases estimated the percentages of CD8+ and CD4+ populations. Analyses of one case (case 5) in the Gray et al *Brain Pathology* article [9] indicated that a majority of T cells were CD8+, with fewer CD4+ cells. In another case (case 4), demyelination was accompanied by p24-immunoreactive cells with robust CD8+ T-cell infiltration, but without detection of CD4+ T cells in the serial section. A few early studies addressed the possibility of CNS-infiltrating T cells expressing both CD4 and CD8, or even acquiring a double-positive phenotype as disease evolves.

In the Lescure et al study, analyses of CSF from 3 cases indicated that the CD8+ cells present were also CD38+. CD38, a glycoprotein expressed on the surface of immature T and B cells, declines as lymphocytes mature, but may be recalled in response to viral challenge [10, 11]. Early studies proposed stage-associated expression patterns of HLA-DR and CD38 on peripheral CD8+ T cells with possible functional correlates to host response to viral infection [12]. A study in HIV-positive children suggested that an increased percentage of CD38+ cells in the peripheral blood population is associated with poor response to antiretrovirals [13]. Thus, the Lescure et al finding suggests that T-cell reactivation is occurring in response to a possible viral stimulus, perhaps low-level HIV replication or expression of HIV proteins such as Tat and Nef [14]. In this context, perhaps even the “weak expression of HIV protein” described by Lescure et al is sufficient to stimulate CD8+ T-cell infiltration into the CNS. Peripheral redistribution of lymphocyte mononuclear cell populations may also encourage the recruitment of immature CD8+CD38+ to the brain in response to existing CNS-derived HIV factors.

Neuropathological findings from stereotactic brain biopsy also identified reactive astrogliosis, microglial activation, p24-immunoreactive cells morphologically similar to microglia or macrophages, and myelin pallor accompanied by foamy macrophages [9], consistent for the most part with HIV-associated leukoencephalopathy; however, the absence of high viral burden in the CNS distinguishes these cases from the leukoencephalopathy series [3]. In addition, although CD8+ T-cell infiltration is reported in CNS IRIS, the cases reported by Lescure et al lack the immune recovery phenotype that is typical of IRIS-like phenomena because no opportunistic pathogen was found.

A recent review by Kranick and Nath addresses the expanding roles of the consulting neurologist in managing HIV patients receiving ART [15]. More potent antiretroviral drugs result in virologic control in the periphery and in CNS, and at least partial recovery of the immune system, but they can also be neurotoxic. Although no clinical estimates of antiretroviral regimen neurotoxicity currently exist, Lescure et al did not find an association among estimates of higher distribution of antiretrovirals into the CNS, the CNS penetration-effectiveness score, and either risk for CD8+ T-cell encephalitis or mortality. Of note, the use of corticosteroids in these cases confounds the relationship between antiretroviral distribution into the brain and neurological outcomes. Lescure et al propose that HIV-associated CD8+ encephalitis is a novel presentation of nervous system disease. They hypothesize that interruption in ART, CSF viral escape, or seemingly trivial coinfections may support or promote the development of this condition that is characterized by CD8+ T-cell infiltration into the brain without high viral burden in the CNS or typical IRIS presentation. Whether this is truly a new entity or simply newly recognized, the cases described here appear to be distinctive and further expand the spectrum of HIV CNS disorders that occur during ART. Of greater concern is the question, “Do these severe cases represent the tip of the pathological iceberg?” In other words, could a milder form of this disorder be smoldering in people who are taking ART and whose only symptom is persistent neurocognitive impairment? While this raises new concerns about the health of the nervous system during ART, it may help explain in part why neurocognitive disorders persist during ART and point the way toward new diagnostic assessments and therapies for HIV-associated neurocognitive disorders.

**Note**

*Potential conflicts of interest.* Both authors: No reported conflicts.

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