Closing in on an infectious etiology of motor neuron disease

The initial report of amyotrophic lateral sclerosis (ALS) complicating HIV infection occurred just 4 years after the first reports of AIDS in 1981. In subsequent years, contrary to the anticipated inexorable progression of motor neuron disease (MND), disease stabilization or recovery was often observed. In 2001, 7 HIV-seropositive individuals with an ALS-like disorder whose MND was reversed with antiretroviral therapy were reported in Neurology®. In an accompanying editorial, Jubelt and Berger remarked that retroviruses were "ideal candidates to cause classic ALS because they replicate by synthesizing a DNA copy (the provirus) that can persist by integration into the host’s cellular DNA." Furthermore, it was noted that HTLV-1, another retrovirus, although typically associated with spastic paraparesis, could be associated with anterior horn cell disease. While attention was focused on HIV as the potential causative retrovirus, Bowen et al. in this issue of Neurology suggest that the association of HIV with MND occurs as a consequence of the activation of the human endogenous retrovirus K (HERV-K) and demonstrate apparent disease stabilization with aggressive antiretroviral treatment that led to a decline in blood HERV-K levels. However, the study was small, conducted in only 5 individuals with HIV infection and MND; in 3, antiretroviral therapy reversed neurologic symptoms and in 2, the disease progression was slowed.

HERVs are proviral remnants originating from ancient retroviruses that had permanently integrated into the germ line of our primate and hominid ancestors, representing 8% of the human genome. Typically, HERV expression is regulated by epigenetic modifications of DNA and host retroviral restriction factors, as well as being targeted by CD8+ T cells; therefore, under normal circumstances, they remain latent. Indeed, HERV expression in the CNS has been associated with neurologic disease in the past, including HIV/AIDS. Infection by HIV may induce the expression of the HERV-K provirus through Tat-mediated transcription activation. Bowen et al. propose that the expression of HERV-K results in MND based on its detection in blood and the correlation of clinical stability of MND in these individuals with antiretroviral therapy and a reduction in the detectable HERV-K levels.

As the late astronomer Carl Sagan said, "Extraordinary claims require extraordinary evidence" and there are a number of future studies that would greatly support the hypothesis that HERV-K expression is related to MND. Potential confirmatory studies include testing the idea that HERV-K expression is specific to individuals with MND and not simply an epiphenomenon of the HIV infection; detecting HERV-K in the CSF of patients with MND; correlating disease course with HERV-K levels in a much larger sample; and developing an HIV-specific animal model for the disease.

Could this observation, if confirmed, be generalizable? Namely, are there individuals who have developed sporadic ALS unassociated with HIV infection in whom the disease is driven by HERV-K? This is an intriguing question that will require a great deal more study. The demonstration of HERV-K activation in cortical neurons and anterior horn cells of patients with sporadic ALS by these same investigators is a tantalizing clue to the possibility, which is reinforced by recent observations from the same group showing that a transgenic mouse expressing neuronal HERV-K env exhibits features of MND. Nonetheless, other groups have reported that HERV-KII exerts neuroprotective effects through neurotrophin induction during HIV infection. The medical community anxiously awaits further evidence clarifying these exciting findings. Until further evidence is forthcoming, individuals with MND unassociated with HIV infection should receive antiretroviral therapy and a reduction in the detectable HERV-K levels.


