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Editorial

HIV related motor neuron disease/syndrome: The - potentially treatable - retroviral link in ALS?

A viral etiology of ALS or at least contribution to its pathophysiology as an environmental risk factor is a plausible proposition, considering the exquisite neurotropism and neurovirulence of some viruses towards motor neurons.

Foremost to mind comes the poliovirus which, like several other enteroviruses (EV), selectively infects motor neurons; with chronic persistent or latent/non-lytic infection it may lead to a clinically ALS-like post-polio syndrome or even contribute in the pathogenesis of sporadic ALS [1]. The clinical and epidemiological data, however, remain inconclusive if not controversial as to a causal relationship between EV and ALS, but promising research continues targeting novel putative molecular mechanisms and proteins like RNA-processing metabolism [1].

The human retroviruses, both exogenous and endogenous have been focus of much attention in the quest for a causative viral pathogen for ALS. Both HTLV-1 (Human T-cell leukemia or T-lymphotropic Virus 1) and HIV-1 (Human Imuno-deficiency Virus 1) are, in addition to their effects on the immune system, strongly implicated in neuropathology including ALS-like syndromes [2]. Reverse transcriptase (RT) activity, found in HIV-uninfected patients with sporadic ALS (and their blood relatives), but not in their spouses or other non-related healthy controls, seems to strongly suggest an inherited, endogenous source of the RT activity, a HERV (Human Endogenous Retrovirus) rather than an exogenous retrovirus acquired through infection [3]. In addition, there are possible interactions or interrelations between HIV and HERV-K in patients with HIV-associated MND as reported by Bowen et al., with HIV-associated MND patients clinically responding to antiretroviral (ARV) therapy showing a corresponding decrease of initially elevated HERV-K levels [4].

Since the 1985 initial report on a patient with HIV and co-occurring ALS [5], there have been several case descriptions and small case series adding up to approximately 33 patients documented by the most recent count [6]. Remarkably there have been a number of HIV-infected patients with MND/ALS whose clinical syndrome stabilized, improved or even resolved on ARVs, implying that immune reconstitution as associated with HIV viral control and normalization of CD4 lymphocyte count can halt or possibly reverse the pathological process affecting the motor neurons [6].

In this issue of JNS, K. Moodley and her co-authors add valuable data and information to the understanding and discussion of HIV-associated MND [7]. Albeit a retrospective chart review it is a comprehensive analysis of HIV-infected and HIV-uninfected MND patients from a high HIV prevalence region, the KwaZulu Natal Province of South Africa. The long study duration of 14 years allowed for a sizeable number of patients from both groups, adding an additional 35 patients with HIV-ALS to the literature. Sufficient longitudinal follow up data was available to determine treatment responses and outcomes in many, making this the largest individual data set on these patients. Key features of HIV-related Motor Neuron Syndrome (MNS) are younger age at onset (typically less than 50 years), a more symmetrical, aggressive and severe clinical and electrophysiological picture at presentation with a shorter duration of history prior to presentation, reactive CSF with elevated lymphocyte count and protein levels, and recovery with ARVs. The Kaplan-Meier survival estimate curve based on follow up data available from 65% (26/35) of the HIV-infected and 85% (86/101) of the HIV-uninfected cohort, shows a statistically significant lower standardized mortality ratio in the HIV-infected category amounting to 50% lower mortality. Early death in the HIV-infected group was associated with patients either ARV naïve or not yet immune reconstituted, indicating that there may be an early therapeutic time window for halting or reversing the disease process. In view of the multistep hypothesis of MND with HIV infection as the putative environmental trigger, this implies that successful treatment with ARVs can lead to termination of the neuro-inflammatory cascade propagated by HIV (and/or HERV-K?), resulting in clinical and electrophysiological recovery of the functional unit of the upper and lower motor neuron [4,8]. This is despite Wallerian degeneration of the corticospinal/bulbar tracts seen on MRI brain in 57% of the HIV-infected MNS patients [7]. The molecular and genetic mechanisms behind this ARV driven process need to be elucidated in order to possibly extrapolate findings to treat HIV-uninfected, potentially HERV-K derived MND.

The study by Moodley et al. also sheds some welcomed light on the epidemiology of MND/ALS in Africa and South Africa in particular. There is a dearth of reliable data from the continent and particularly sub-Saharan Africa [9,10]. The study population can be separated by race groups into Black African, Indian and European descent according to the locally predominant groups. By population statistics Black Africans far outnumber the other race groups. Thus the majority of the study population was Black African. Prevalence analysis by race group in the literature depicts lower rates in populations of mixed ancestry compared to Europeans coupled with somewhat earlier age of onset in the former [10]. HIV-uninfected MND race adjusted prevalence rate per 100,000 was 0.44 among black Africans, 4.1 among Indians and 4.4 among Whites. With age standardization and adjustment for race, MND (HIV-uninfected) prevalence in elderly Whites was 8-12/100000 compared to 3.9/100000 in elderly Blacks, concurring with the experience from the literature [10]. Comparisons between HIV-uninfected MND and HIV-infected MNS were only possible for the Black race group as there were only 1 White and Indian HIV-infected MNS patient respectively. The race adjusted prevalence rate for HIV-MNS was 2.4/100000, so fivefold that of HIV-negative MND in Blacks. However, this may merely represent a reflection of the demographics of the South African HIV epidemic which mainly affects young Black Africans. The age adjusted prevalence rate in the HIV-MNS category was 1.66/100000 in

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Blacks under the age of 50 years, compared to 0.36/100000 for the same age category in Black MND patients, clearly pointing towards HIV infection as the causal confounder.

Without doubt HIV infection ought to be added to the list of causes of a potentially reversible and treatable ALS syndrome and HIV should routinely be tested for in the relevant setting, particularly in high prevalence regions like sub-Saharan Africa. Upon extrapolation of the data from the South African study, there should be many a case of HIV-MNS, hopefully receiving the correct diagnosis and early ARV treatment in these mostly under-resourced regions.

Clearly the authors make a strong case for a retroviral etiology of ALS and the article will certainly rekindle if not re-ignite the debate among both patients with ALS and their caregivers and physicians whether or not to treat with ARVs. The key questions remain, what is the pathogenic role or contribution of HERV-K within the "multistep hypothesis" of MND/ALS, and are our HIV antiretroviral drugs or drug combinations effective to inhibit the HERV lifecycle or reduce HERV gene expression.

There are two published trials on ARVs in ALS patients, one with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine from 1992, the other one with the protease inhibitor (PI) indinavir from 2005 [11]. Both these monotherapy trials were negative and because adequate HIV control requires combination ARV therapy, it is reasonable to assume that the trials were negative for that reason. There is in vitro evidence that HERV-K might be best susceptible to most NRTIs, but is possibly resistant to PIs; there is mixed evidence regarding non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase inhibitors (INSTIs) [11]. Furthermore the ARV CNS penetration effectiveness (CPE) needs to be considered in the deliberations on ARVs for HERV control. The routine ARV combination used in the present study for the HIV infected MNS patients consisted of the NRTIs stavudine and lamivudine, and the NNRTI efavirenz.

The "ALS community" is eagerly awaiting the publication of the outcomes of the two currently ongoing trials in this field of ARVs, HERV-K and MND:

"HERV-K Suppression Using Antiretroviral Therapy in Volunteers With Amyotrophic Lateral Sclerosis (ALS)", a US based Phase 1 proof of concept study using Genvoya (darunavir, ritonavir, raltegravir, zidovudine) [12], and "Safety and Tolerability of Antiretroviral (Triumeq) in Patients With Amyotrophic Lateral Sclerosis (ALS)", an Australian Phase 2a open label study using Triumeq (dolutegravir, abacavir, lamivudine) [13].

With more in vitro and in vivo evidence coming to the fore, larger studies and bigger clinical trials on ARVs for patients with ALS are much needed.

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