Human Immunodeficiency Virus and Multiple Sclerosis Risk: Probing for a Connection

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Abstract

Multiple Sclerosis (MS) is a chronic autoimmune inflammatory disease of the nervous system, with intense genetic and environmental background. Its etiology is poorly understood and likely multifactorial but its epidemiology has been intensively studied. This complex disease displays heterogeneity in terms of geographic and genetic influences on incidence, insinuating an effect of local unknown environmental factors on its development. Among numerous potential factors putatively involved in the etiopathogenesis of MS, retroviruses appear to influence MS. The intent of this review is to highlight the association between human immunodeficiency virus (HIV) and the risk of developing MS while at the same time providing an overview of the insights gleaned from different studies. HIV infection is associated with a reduced risk of MS development, and perhaps, appears to be another wedge of the MS conundrum. The probable mechanisms for this relationship may be suppression of the immune system and/or antiretroviral drug therapy. While highlighting the relevance of antiretroviral medications as potential future alternatives for the effective treatment of MS, this review provides an impetus for further studies. We conclude that studies in this milieu hitherto are insufficient, and there is need for an upsurge in molecular epidemiological and clinical studies, with focus on the mechanism behind the impact of HIV/antiretroviral drugs on MS. Such inquiry could precisely establish the causes for associations between HIV and MS, perhaps impacting treatment options for both.

Keywords: MS; Autoimmune; Inflammation; Epidemiology; Environmental factors; HIV

Abbreviations

ART-Antiretroviral Therapy; CNS-Central Nervous System; DMTs-Disease Modifying Treatments; HERV-Human Endogenous Retroviruses; HHV-6-Human Herpes Virus-6; HIV-Human Immunodeficiency Virus; MS-Multiple Sclerosis.

Introduction

Multiple Sclerosis (MS) is a neurological disease affecting the Central Nervous System (CNS) caused by an immune attack against the fatty myelin sheath around the axons of CNS, leading to demyelination [1]. Its prevalence is more common in the young between ages 20 and 40 and occurs more often in women than in men [1,2]. It is accompanied by a wide continuum of signs and symptoms with a profound effect on the communication between nerve cells inside the brain and spinal cord [1]. Although there is incomplete understanding of the basic mechanisms behind MS pathogenesis, evidence suggests heterogeneous etiologies of MS, implying the role of multiple environmental factors in its course and development [3-5].

A significant proportion of studies have shown that risk factors such as candidate genes [6,7], smoking [8-10], geographic location[11,12], viral infections [13-17], wheat consumption[11, 18], dairy product consumption[19,20], fish intake [21], animal fat intake [21], high ultraviolet radiation [22-24] and Vitamin D [25-27] amplify the risk of developing MS or its progression. They might work in synchrony with other risk factors and genes, thus leading to disease onset. Various studies suggest that, in eliciting MS, there occur intricate interactions between genetic factors and various other factors, including infectious agents (Figure 1) [28,29]. The connection between genetic and infectious components is exemplified by the human endogenous retroviruses (HERV) [30,31]. Viral infections sometimes trigger exacerbations of MS and can lead to direct damage of oligodendroglia and T cells [32]. The suggestive substantiation for the role of viral infections in MS can be exemplified by the presence of oligoclonal bands in the brain and Cerebrospinal Fluid (CSF), the role of many viruses in human demyelination encephalomyelitis, and the generation of demyelination in animals [32].
Figure 1: Multiple Sclerosis as a multifactorial disorder. Interactions between genetic and environmental component leads to MS, thus making it a complex and heterogeneous disease.

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**HIV Connection with MS**

HERV makes up 10% to 30% of the human genome; however, detection of these viruses or their proteins is probably a consequence of immune activation, not the cause of the disease [33,34]. Among copious reports of viruses hypothesized to play a role in MS etiology, a notable proportion of recent studies now focus on retroviruses. Recent studies suggest Human Immunodeficiency Virus (HIV) infection to be inversely related to MS risk [35-37] but, to date, the association between the two remains enigmatic. Nevertheless, the most noteworthy evidence for the HERV link to MS comes from this association [36,38].

Although MS and HIV are among the most widely reported and discussed conditions today, there is only a single case report of an MS patient with HIV, treated with antiretroviral medications. The patient’s HIV symptoms disappeared after 12 months, and he did not experience MS-related signs and symptoms for over a decade [38]. Subsequently, an epidemiologic study showed diminished incidence of MS in HIV patients by means of population-based databases; however, the apparent observation was statistically insignificant due to the small number of cases and controls [35]. To further investigate the possible association between HIV and MS, a recent study explored a much larger sample, finding that HIV infection leads to a notable reduction in the risk of developing MS[36]. With hospital based data from 1999 to 2011, comparison of 21,207HIV patients with a wider group of more than 5 million controls indicated that HIV patients were 62% less likely to develop MS. Additionally, it was concluded that the protective effect of HIV on MS appears to be mediated by the immunosuppression induced by chronic HIV infection and antiretroviral therapy (ART). This hypothesis is supported by the fact that, even in the absence of ART, HIV per se can cause immune dysfunction by hampering homeostasis within immune cells and targets pathways linked with MS pathogenesis (Figure 2). Also, antiretroviral drugs used for HIV treatment may inadvertently smother other pathogens correlated with MS, such as herpes viruses and HERVs, as a consequence of which MS development is either halted or ameliorated [39]. Although the negative association between HIV and MS reveals a protective effect of HIV against MS, the appropriate mechanism behind this relationship at present cannot be explained by this study due to unavailability of information on the mode of HIV treatment in the database analyzed. It remains uncertain whether HIV, ART, or a combination of the two plays a role in preventing or treating MS.

Although there are some weaknesses in Gold et al study, by and large, it is statistically the most significant study which has analyzed one of the world’s largest linked medical data sets. Its results thus have made a considerable contribution to the literature on the potential relationship between HIV and MS development. Yet the precise association between HIV and MS still remains unresolved. For enhanced understanding of the basic mechanisms behind the role of
HERV in MS, there are no workable cell cultures or animal model for examining this hypothesis. Nevertheless, a clinical study on the antiretroviral drug Raltegravir and a monoclonal antibody (GNbAC1) specific for HERV proteins is already underway with MS patients [40-43].

Recent reports have revealed that MS patients treated with GNbAC1 showed signs of improvement, which suggests neuroprotective attributes of GNbAC1, thus supporting its potential as a safe, promising and better long-term treatment option for MS patients [41-43].

The escalating indication of an association between HIV and MS warrants further investigation. Larger cohort studies will broaden our understanding of mechanisms, as this is imperative because understanding the role of HIV/ART may provide fruitful insight into the development of therapeutic alternatives. This review provides the much needed ground for conducting further research on HIV/ART and MS, to facilitate explicating the exact mechanism behind this association and elaborating the precise role of HIV in reducing the risk of MS development. It is astonishing that, despite the availability of ART from so many years, hitherto, no cases of patients with both MS and HIV were identified for this review. It is also ironic that, inspite of the fact that both MS and HIV impinge on the immune system, there are no documented guidelines on the usage of disease modifying treatments (DMTs) for MS management in patients who are already on ART for HIV treatment [36].Nevertheless, to reach some logical conclusions, more attention is needed to systematically look into other aspects of relationship between antiretroviral medications and MS development. To unravel and understand this conundrum, additional research, both large-scale epidemiological studies and clinical trials, are necessary to explicate the interactions between HIV and MS, and also make therapeutic use of the contributory mechanistic role of HIV/ART in lowering the risk of developing MS.

Conclusions

Regardless of the extensive research on MS, its exact etiology remains elusive, and epidemiological findings across the globe indicate its association with specific retroviruses endogenous to humans. There is paucity of reports on HIV and MS association, and further research is therefore needed to corroborate and explain this association. This review describes the research on the association between HIV and risk of developing MS. In light of the above discussed literature, this review provides further edifying substantiation to support the perception that there is an association between HIV (or its treatment) and a reduced risk of MS; however, it is evident that this association needs to be examined sceptically. At the same time, an upsurge in investigation is warranted to further scrutinize and unscramble this relationship. Research is needed to definitively determine whether having HIV, being treated for HIV with antiretroviral medications, or the combination of the two reduces the risk of developing MS. Eventually, this research will likely aid in using antiretroviral drugs as potential...
treatment options for MS and devising more promising strategies for MS management.

References


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