Chapter 7

Association Between Multiple Sclerosis Risk and Human Immunodeficiency Virus Infection: Insights and Challenges

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Abstract

Multiple sclerosis (MS) is a convoluted autoimmune and inflammatory disease of the central nervous system (CNS) in which the protective myelin sheath is eroded and the underlying nerve fibers are damaged. There is no conclusive knowledge on the role played by different etiological factors in its development, and studies have shown that it primarily results due to complex interactions between the genetic, geographic and infectious components. Among the risk factors reported to have a possible role in MS development, retroviruses also appear to influence it. Studies suggest human immunodeficiency virus (HIV) infection to be inversely related to MS risk, but to date, the association between the two remains enigmatic. This protective inverse association has become an area of active research and the most plausible explanations for this may be immune suppression and/or antiretroviral medications. The purpose of writing this chapter is to provide background information on the unfathomable relationship between HIV infection and the risk of developing MS while at the same time providing description of the insights garnered from recent studies. While highlighting the application of ART (antiretroviral therapy) as budding future alternative for MS management, this chapter provides momentum for further studies.

Keywords: multiple sclerosis, etiology, human immunodeficiency virus, epidemiology, ART

1. Introduction

Multiple sclerosis (MS) is a complex, debilitating neurologic disease characterized by demyelination of axons in the brain and spinal cord and caused by an immune attack against the myelin sheath. The disease is highly prevalent in North America and Europe (>100/100,000 inhabitants). According to the recently revised 2013 Atlas of MS published by the World Health Organization (WHO) and Multiple Sclerosis International Federation (MSIF) (http://www.atlasofms.org), the prevalence rate of 5–20 per 100,000 has been reported for India. Clinically, MS is characterized by a broad spectrum of symptoms [1]. It has autoimmune and inflammatory components, with intense effects on the communication between nerve cells within the brain and spinal cord [1]. The different types of MS vary in terms of severity, prevalence, and degree of progression [2, 3]. The most common phenotype is relapsing remitting (RR) MS, followed by secondary progressive (SP) and then primary progressive (PP). Less prevalent phenotypes have also been reported [2]. MS pathology is characterized by inflammatory plaques caused by demyelination of axons in the central nervous system (CNS). Due to the presence of immune-inflammatory characteristics in MS, treatments targeting T lymphocyte and natural killer (NK) cell activation seem to play a significant role [4].

With intangible and enigmatic etiology having both genetic and environmental backgrounds, MS offers a profound conundrum. Yet, despite incomplete understanding of the basic mechanisms behind its pathogenesis, a growing body of evidence suggests heterogeneous etiology of MS with multiple environmental factors contributing to its development [5–7]. Various studies suggest that intricate interactions between genetic factors and environmental factors elicit it; thus, genetically susceptible individuals who encounter a number of environmental and epigenetic factors are at higher risk (**Figure 1**) [8, 9].

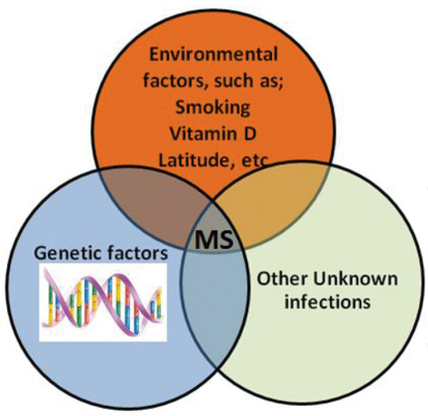

Figure 1. Multiple sclerosis as a complex neurological condition affecting CNS: The etiology of MS is unknown and enigmatic; however, it has a profound role of numerous environmental and genetic components, and multiplex interactions between them lead to its development, thus making it a multifactorial and polygenic heterogeneous disease.

Some risk factors, which have been studied in various populations, include geographic location [10, 11], wheat consumption [11, 12], dairy product consumption [13, 14], fish intake [15], animal fat intake [15], high ultraviolet radiation [16–18], vitamin D deficiency [19], and

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viral infection [20–22]. The likely association between genetic and infectious components in MS development is shown by the human endogenous retroviruses (HERVs) [23, 24]. Although many viruses have raised suspicions as responsible for MS, not all studies confirm their etiologic role. Thus, each virus has chalked up another obstruction in the MS conundrum. There is escalating evidence suggesting a retroviral connection to MS risk, and the most noteworthy among them is human immunodeficiency virus (HIV). Studies suggest HIV infection to be inversely related to MS risk [25–27] but, to date, the association between the two remains enigmatic [28]. The purpose of this chapter is to provide an overview of the insights garnered from recent studies on the association between HIV and MS risk. While highlighting this association, the main objective of this chapter is to provide an impetus for future studies aimed at precisely establishing the mechanism behind the impact of HIV on MS.

2. Link between HIV and MS risk

The epidemiology of MS shows a latitudinal gradient, and its risk is governed by genetic predisposition as well as local environmental conditions (**Figure 1**). Even though its etiology remains uncertain, quite a few studies have suggested involvement of a virus in its pathogenesis. For example, the association between genetic and infectious components in MS development is suggested by the HERV, which constitutes about 8–30% of the human genome with approximately 98,000 elements [29]. Until 2005, however, no HERVs capable of replication had been identified, only traces of original viruses were identified [30]. were identified. Only one family of HERV viruses has been active, the HERV-K family, comprising <1% of total HERV elements [29, 30]. This family is a candidate for playing a fundamental role in MS pathophysiology. Evidence for this role includes studies that have shown activation of T-cell response against HERV in individuals infected with HIV [31]. This has formed the much needed ground for alternative drug therapy targeted against HERV for elimination of HIV, and it might therefore aid in using HERV proteins as markers for drug designing instead of frequently mutating HIV antigens. One of the HERV proteins reported to be expressed in the active lesions of MS is the MS-associated retrovirus envelope protein (MSRV-Env) [32–34]. There is accumulating evidence suggesting an inverse association between HIV and MS, and large-scale epidemiological studies have supported this notion. Studies have found significantly lower prevalence of MS in people with HIV infection [26]; moreover, there has been only a single case report of MS treatment with antiretroviral drugs in an HIV patient.

With the help of population-based databases, a recent study demonstrated reduced incidence of MS in HIV patients; however, due to a smaller sample size, it proved statistically insignificant [26]. Gold et al. [25] investigated a much larger sample and revealed a statistically significant negative relationship between HIV and MS, reflecting a protective effect of HIV on MS. Still unclear is the exact mechanism behind this association. The protection HIV provides against MS may be mediated by suppression of the immune system due to chronic HIV infection and antiretroviral medications, thus preventing MS progression or treating it completely (**Figure 2**). To date, it is not known whether HIV *per se*, application of antiretroviral therapy (ART), or a combination of the two diminishes MS symptoms. The most plausible

explanation for this protective effect may be HIV-induced immunodeficiency targeting a wide continuum of immune cells and signal transduction pathways involved in MS pathogenesis. Alternatively, antiretroviral medications used against HIV may target other viruses involved in MS pathogenesis such as, HERV and herpes.

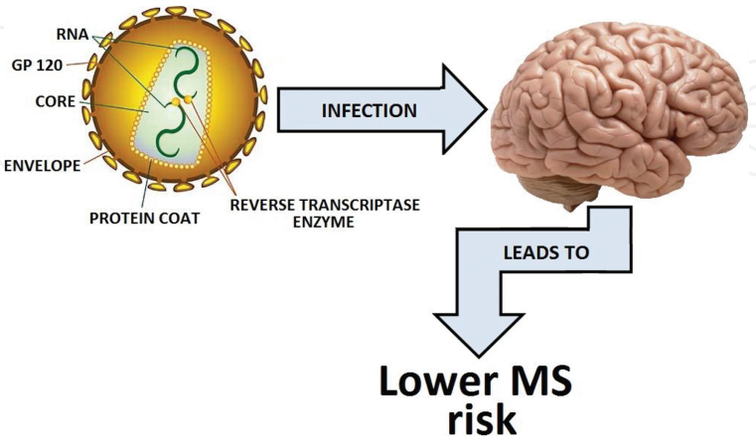

Figure 2. Protective inverse relationship between MS and HIV: HIV infection leads to reduced MS risk, which may be attributed to constant suppression of the immune system by HIV-induced immunodeficiency targeting diverse spectrum of immune cells and signal transduction pathways involved in MS pathogenesis, and/or antiretroviral drugs used to treat the infection, thus preventing MS progression or treating it completely.

The big puzzle of whether and when to start HIV therapy in MS patients remains blurred. Previous studies based on case report and data linkage studies presumed that protective infection was conferred against MS development due to ART treatment rather than HIV infection *per se*. However, in neither case has systematic description been offered about the individuals who were treated with ART and those who were not [27]. There are still different opinions on early [35] and late treatment options due to different aspects such as side effects and drug resistance [36]. Therefore, no clear-cut approach exists on starting ART. In these studies, nothing has been mentioned about exposure to antiretroviral medications and its duration [27]. Moreover, HIV and MS are often misdiagnosed due to the presence of MS-like symptoms in HIV; therefore, focus should be on targeted treatments of MS patients with HIV and vice versa. To fully understand the mechanism behind the apparently MS-protective phenotype of HIV infection, the most plausible research approach would be analysis of data on HIV patients with MS or vice versa and the details on influence of cotreatment with antiretroviral medications and disease-modifying treatments (DMTs).

Due to the presence of immune-inflammatory characteristics in MS, treatments targeting T lymphocyte activation may play a significant role. There is growing evidence that favors suppression of MS pathology by employing anti-HIV therapy, and it has prompted one trial in MS patients for the drug Raltegravir (Isentress) [37] used in HIV treatment and also an immunoglobulin G4 monoclonal antibody called GNbAC1 [4, 38–40] against HERV proteins. The association between HIV and MS can be exploited to replace conventional treatment options for MS by formulating new safe, effective, and long-term therapeutic alternatives. Further investigations are mandatory to provide a deeper insight into the mechanism of action

for HIV/ART on MS risk, and this can be fulfilled by carrying out large-scale clinical, molecular, as well as epidemiological studies.

3. Conclusion

Despite the extensive research on MS, its exact etiology remains hard to pin down. Nevertheless, epidemiological findings across the globe suggest its association with specific retroviruses endogenous to humans. Regardless of the paucity of reports on HIV and MS association, this finding appears to be crucial in the etiology of MS. A comprehensive understanding of this link is needed to elucidate the complex interactions between HIV and MS and also to exploit HIV's protective role in order to develop treatments for MS. Research that unscrambles the relation between the two would, at the same time, provide new insights into the etiopathogenesis of MS and provide therapeutic targets and strategies.

Nevertheless, additional studies on mechanisms of interaction between HIV and MS are required to determine the underlying mediators of this protective association and eventually endow insight into the disease pathogenesis as well as its management. To date, the studies in this milieu hitherto are insufficient, and there is extreme need for an extensive upsurge in large-scale conclusive molecular and epidemiological studies. It is noteworthy that this chapter further enlightens the acuity of an association between HIV (or its treatment) and a reduced risk of developing MS; however, it is flagrant that this association needs to be examined skeptically in order to gain deeper insight into this enigmatic relationship. The need of hour is to establish precisely whether having HIV, being treated for HIV with antiretroviral drugs, or a combination of the two reduces the risk of developing MS, which will certainly open the door for developing better and more promising treatment options for MS.

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