

Review Article

Alcohol and multiple sclerosis: an immune system-based review

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Abstract: Multiple sclerosis is a chronic inflammatory disease of the central nervous system (CNS). Although the exact etiology of multiple sclerosis is unknown, researchers suggest that genetic, environmental, and microbial factors play a central role in causing multiple sclerosis. Pathology of multiple sclerosis is based on inflammation as T cells enter the brain via disruptions in the blood-brain barrier, recognizing myelin as foreign antigen; and as a result, the T cells attack myelin and start the inflammatory processes, enhancing inflammatory cytokines and antibodies. Since previous studies show ethanol can suppress the immune system such as innate, humoral, and cellular immunity and increases the production of anti-inflammatory cytokines, we hypothesized maybe ethanol also have ameliorating effects on multiple sclerosis symptoms. Although alcohol induces apoptosis in oligodendrocytes and neurons, causing demyelination and affects CNS directly, in this study we will investigate ethanol's effects on some aspects of the immune system in multiple sclerosis.

Keywords: Alcohol, multiple sclerosis, immune system

Introduction

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system (CNS) [1, 2]. Briefly, MS can be described with demyelination that mostly affects CNS including spinal cord and brain and in few cases; it has been found that MS has affected the peripheral nervous system (PNS). Although many investigations have been done to determine the relationship between MS and some possible factors such as environment, genetics, and infection history until now there has been no exact evidence about etiology of MS [3, 4]. Studies on viruses such as HBV, EBV, HSV, and HHV indicate that perhaps viral infection increases susceptibility to MS [5]. HLA genes, especially HLA B1501, are the genes that associate with MS strongly [6]. Also, there are other genes such as cytokine gene which attention about them has increased [7]. Vitamin D and also histamine is also proven to have a significant association with MS [8, 9]. Along

with the mentioned factors, weather, environmental pollution, job, diet, smoking, and lifestyle are other factors, which affect the epidemiological distribution of MS [10]. The most widely recognized mechanism for the pathogenesis of MS is based on auto-reactivity of T cells against glycoproteins of myelin [11]. Normally, the immune system protects the body against internal and external risk factors. Internal violators are cells that their proliferation is out of control, and external factors mostly include infectious agents. Although recessive tolerance prevents entrance of auto-reactive lymphocytes into the peripheral lymphoid organs, sometimes, recessive tolerance cannot recognize a few of these auto-reactive lymphocytes [12, 13]. Specific auto-antigens activate auto-reactive lymphocytes and when the condition of the immune system is appropriate for auto-reactivity, they develop autoimmune disease [14]. One of the T cell subtypes, which is named T regulatory cell (Treg), is responsible for prominent tolerance [15]. Tregs suppress auto-reactive lymphocytes mainly by cytokine production

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[16]. Differences in types of alcohol, duration of alcohol consumption, gender, and age cause different effects of alcohol on the immune system [17]. Furthermore, nutritional deficiency, a common manifestation of alcohol consumption, weakens the immune system [18]. Alcohol weakens many parts of the immune system such as thymus, spleen, humoral and cellular immune responses [19]; it induces apoptosis in brain neurons and is also associated with cell damage in the CNS, and interfering with myelin synthesis of oligodendrocytes [18, 20].

As the aforementioned data suggest, we observe the role of auto-reactive T cells and B cells, inflammatory cytokines and an increase in activities of natural killer cells and APC in multiple sclerosis patients. The above data further suggest that chronic alcohol consumption has adverse effects on the immune system by weakening it. As a result, it can be suggested that alcohol consumption can ameliorate multiple sclerosis symptoms. Although alcohol has direct effects on the CNS, in the present review, we briefly describe some immunological effects of alcohol on multiple sclerosis.

Lymphocytes

The detection of myelin-specific T cells in both MS patients and healthy group in previous researches suggest a new concept based on these cells' relevance in MS. These myelin-specific T cells of MS patients are observed as having a phenotype like TH1 cells, validating the idea that these cells might have a pathogenic role in multiple sclerosis disease [21]. Based on several observations, myelin-specific T cells were found in healthy groups; however, they were shown to be naïve lymphocytes; with activated and memory cells of this type of T cells found in MS patients. This data indicates that myelin-specific T cells had been activated in vivo long before the onset of the symptoms. It has been indicated that inflammatory destruction in the patients' CNS is driven by antigen-specific targeting of myelin and other CNS components; based on the presence of the auto-reactive lymphocytes within bordering areas and plaques [22]. Adaptive immune responses, which are occurring by T lymphocytes particularly, are thought to mediate the damage of myelin and nerves within the cerebrospinal fluid (CSF) in MS pathogenicity [23]. Huge investigations have been promoted to under-

stand the potential CD4 T cell targets in MS to determine whether EAE can be mediated by CD4 T cells or not.

Providing an altered peptide ligand of MBP designed for therapeutic suppression of CD4 T cell, responses marked the importance of antigen-specific CD4 T cell responses in MS, the results of which showed disease exacerbations in multiple patients [24]. Auto-reactive cells, particularly, and in general, T cells from MS patients them can recognize a variety of myelin protein targets, including MBP, PLP, MOG and MOBP [25], among others. Non-myelin T cell antigens have also been described, including α B crystalline 6 and neuronal proteins such as contactin-2 [26]. Auto-reactive CD8 T cell is also observed [27], in addition to myelin-specific T cell avidity and activation profiles appear to be elevated in MS patients, although similar frequencies of auto-reactive T cells are demonstrated in MS patients and healthy group [28].

There are oligoclonal bands in MS, found in the cerebrospinal fluid (CSF) [29], presenting Immunoglobulins which are locally produced by plasma cells. The mechanism by which these antigens are being recognized by immunoglobulins that present the oligoclonal bands is still a mystery and a lot of work has been done to clarify their pathophysiological impact [30]. The oligoclonal bands have been helpful biomarkers for diagnosis, so far. Presence of B cell follicles has been noted in the meninges of some patients [31]. In serum and CSF of some patients, Myelin-specific autoantibodies can be tracked as well [32]. In addition, autoantibodies can be associated with myelin debris in situ [33]. Macrophages phagocytize opsonized myelin debris. Amazingly, in many lesions in the CNS, immunoglobulin and complement activation is seen [34]. Additionally, it has been suggested that some patients respond clinically to plasma exchange, suggesting that B cells have an important role in MS pathogenesis, importantly anti-CD20 mAb treatment leads to disease amelioration [35]. Decreased lymphocytic cell numbers in the circulating blood have been consistently shown in researches indicating lymphocytes and lymphocyte subpopulations in chronic alcoholics [36]. Likely, decreased the size and cell number in the thymus, spleen, and lymph nodes were the results of chronic alcohol feeding of mice [37]. A suggested mechanism for this phenomenon is programmed cell death

(apoptosis), even though the mechanism of decreasing lymphoid cell count by alcohol is still unknown [38]. Increased apoptosis of thymocytes is the result of acute ethanol treatment [39]. Following acute ethanol treatment, increased apoptosis was also seen in human blood mononuclear cells [40]. A decrease in lymphoid cells count has been demonstrated in addition to weakened proliferation procedures, which lead to the idea that ethanol-exposed lymphocytes might have less power for proliferation and differentiation in response to an antigenic challenge [41]. Effects of ethanol on protein kinase C were demonstrated as a probable mechanism for defects of T cell proliferation [42]. In chronic alcoholics, creased delayed-type hypersensitivity response and immune abnormalities have been demonstrated [43]. While the function of B lymphocytes appear to be impaired in alcoholics, increased mitogen-inducing in a murine model of acute alcohol intake in vivo showed immunoglobulin production in the alcohol-treated group [44]. The exact number of B cells is the same in non-alcoholic individuals [18].

NK cells

Considering higher NK cell activity, it might lead to a higher risk of developing active lesions in relapsing-remitting multiple sclerosis (RRMS) patients [45, 46]. In addition, enhancement of T-cell activation can occur in the development of NK cells, which is promoted by IL-12, which is produced by astrocytes. Furthermore, increased IFN- γ secretion by NK cells occurs by the production of IL-18 during the primary injection of antigens [47]. Auto-reactive Th1 responses are activated by IFN- γ , whereas a weakened potential of NK cells to release IFN- γ is a major mechanism underlying resistance to EAE [48, 49]. It has been observed in several types of research that depleting NK cells with specific antibodies lead to decreased EAE clinical disease [50]. Chronic exposure of rodents to ethanol has been shown to results in a reduction of the amount and activity of large granular lymphocyte/NK cells. Presence of ethanol in vitro can suppress the activity of NK cells [51]. Declined frequency of activated NK cells has been reported in peripheral blood in chronic alcoholic humans.

APCs

For pathogenesis of murine models of MS, antigen-presenting cells (APCs) are essential. APCs

present antigen to naïve T cells into lymph nodes, where they mature and travel. This phenomenon is used for example in encountering myelin antigens [52]. Two signals from APCs are needed for T cell activation and survival: presentation of antigen by the major histocompatibility complex to the T cell receptor and a secondary signal provided by the interaction of costimulatory molecules such as CD80 and CD86 with CD28 on T cells. Actually, T cell differentiation into mature effector CD4+ T cell subsets (Th1, Th2, Th17, Treg) during the activation period, relies on the cytokines which are produced by APCs [53]. Recent data demonstrates that both TH1 and TH17 subsets are the factors that cause MS to be driven, though each one differs mechanically from the other [54]. As soon as activation happens, T cells travel to the brain and cross the blood-brain barrier (BBB) where monocytes, macrophages, and dendritic cells are meaningfully more potent in antigen presentation and antigen-specific T-cell activation [54]. Alcohol consuming individuals have been indicated with Impaired delayed-type hypersensitivity response [55] and it also has been shown in a mouse model of chronic alcohol administration. It has been recently suggested that In humans, after one occasion of alcohol intake, a decrease in monocyte antigen-presenting cell function has been observed. Mitogen stimulation or super antigens induce T-cell proliferation, and this induction declined after alcohol consumption and these effects were mediated by alcohol exposure of the antigen presenting cells, monocytes. In humans, after acute alcohol intake or in vitro alcohol treatment, classical antigen presentation by monocytes becomes impaired. Also an inhibitory effect of alcohol on dendritic cell function has been found based on recent researches on various dendritic cell (DC) types. It is observed in human studies that both acute alcohol intake and prolonged in vitro alcohol treatment, inhibited monocyte-derived myeloid dendritic cell capacity to induce T-cell activation. There was also an association between this phenomenon and increased the production of IL-10 and decreased production of IL-12 by alcohol-exposed DCs. In addition, T-cell anergy induced by alcohol-treated dendritic cells resulted in impaired T-cell proliferation even with subsequent stimulation with normal DCs; however, by addition of exogenous IL-12, this T-cell anergy could be ameliorated. Affected functions in the mice skin have been shown to be due to chronic alcohol consumption. There

were also declined amount and migration of Langerhans cells (skin DCs) and dermal DCs in mice with chronic alcohol consumption [56]. Decreased bone marrow-derived DC generation has also been reported to be due to alcohol consumption in mice, as well as decreased expression of the co-stimulatory molecules CD80, CD86, and DCs and impaired induction of T-cell proliferation and IL-12 production [57]. These matters were in a correlation with increased DC production of IL-10, a cytokine with inhibitory actions on DC maturation, antigen presentation, and T-cell proliferation. Chronic alcohol consumption altered CD11c+, CD8+, DC function, and antigen presentation that was associated with decreased levels of IL-6, IL-12 and increased levels of IL-13 cytokine production, which was found on another research [58]. All in all, acute or chronic, alcohol consumption appears to inhibit differentiation and functions of various types of dendritic cells which are concluded from all these results based on recent studies.

Cytokines

Different cytokines participate in Th1 and Th2 responses; for example, Th1 cytokines mostly derive from Th1 cells and macrophages and include IL1, IL2, IL6, IL12, IFN gamma, and TNF alpha; on the other hand, IL4, IL5, IL10, and IL13 have a role in Th2 reactions [12, 59, 60]. Since Th1 cells affect many aspects of MS pathogenesis, such as demyelination and inflammation, they play a significant role in MS [61, 62]. In contrast with Th1 cytokines, Th2 cytokines such as IL4, IL5, and IL10 improve MS clinical symptoms by suppressing Th1 effects in inflammation and demyelination [63-65].

Inflammatory cytokines

Presence of inflammatory cytokines such as IFN-gamma in CNS and involvement of them in demyelination proposes the possible role of IFN-gamma in the pathogenesis of multiple sclerosis and other neuroimmunological diseases [66]. Although the presence of IFN-gamma in the CNS of multiple sclerosis was shown, there is no evidence for the detection of it in the CNS of healthy people [67, 68]. Neutralizing IFN-gamma with anti-IFN-gamma antibodies can reduce disability in MS patients and it can be chosen as a treatment, and using IFN-gamma for MS patients has a direct effect

on CNS inflammation and worsens symptoms of the disease [69]. Elevated levels of IFN-gamma in the CNS affect myelin formation and oligodendrocyte death [70, 71]. Although IFN-gamma causes inflammation in MS patients, recently one study showed that low levels of IFN-gamma during the recovery phase of EAE inhibit myelin formation and oligodendrocyte regeneration [72]. On the other hand, there is no significant relationship between IFN-gamma gene or its receptor gene integrity and risk of EAE, and in some cases these mutations in IFN-gamma gene increase number of deaths among EAE mice [73, 74]. Some studies have shown that prevention of axonal damage, demyelination and oligodendrocyte death can be possible through neutralization of IFN-gamma in CNS before initiation of EAE [75].

Studies that have been done on CNS of human and mice have shown that TNF-alpha like IFN-gamma results in inflammation, and it can also exacerbate demyelination. Surveys on CNS of MS patients detected macrophages and astrocytes that produce TNF-alpha, most of them being in plaques [76]. Similarly, another study clarified that T cells and microglia plaques, and also TNF-alpha and TNF-beta were found in MS plaques. There are many relationships between TNF-alpha and MS, such as high levels of TNF-alpha in both blood and CNS of MS patients causes blood brain-barrier damage, therefore making it possible for auto-reactive T cells to enter CNS as a result [65, 77]. Antibodies against TNF-alpha can preclude the ability of encephalitogenic T cells to distribute EAE among mice [78]. Entrance of inflammatory cells into the CNS, myelin damage and symptoms of EAE can be reduced with the consumption of a soluble type of TNF-r1 [79]. TNF-alpha affects many types of CNS cells such as astrocytes, oligodendrocytes, endothelial cells of the brain, so it intervenes in many aspects of CNS functions. In vitro studies have shown that TNF-alpha has a significant role in the inhibition of myelin formation and oligodendrocyte regeneration [80, 81]. All the effects of TNF-alpha on MS are carried out by direct roles of it in myelin formation and oligodendrocyte regeneration [82]. Chronic alcohol consumption reduces IFN-gamma levels; making this role considered as an important factor for the immune system.

Cooperation between IL-12, which is produced by macrophages and IFN-gamma, is essential for activation of cellular immune responses,

especially Th1-type reactions [83]. Furthermore, a study that was carried out on IL-12 showed that chronic alcohol consumption can reduce Th1-type immune responses and IFN-gamma levels. Another study in this regard showed that IL-12 improves delayed-type hypersensitivity response in mice that consumed alcohol chronically [84]. Although chronic alcohol consumers show decreased response to the pathogens, acute alcohol consumption stimulates these responses. Experiments on humans and mice have shown that bacterial pathogens cannot induce the production of inflammatory cytokines in acute consumers like healthy people [85]. Almost all types of bacteria, including gram-positive and gram-negative bacteria, stimulate the production of IL-1, IL-6, and TNF-alpha at a lower level in cases with alcohol exposure as ethanol reduces their protein and mRNA synthesis [86].

Anti-inflammatory cytokines

It has been shown that IL-10 can protect blood-brain barrier against damages [87] and also inhibit the progression of EAE in mice [88, 89]. Perhaps IL-10 has a role in the remission phase of multiple sclerosis patients as IL-10 levels were higher in proteolipid protein stimulate the culture of MS patients who were in remission phase than MS patients who were in progressive phase or control subjects [89]. IL-4 is another cytokine, which can play a protecting role against autoimmune diseases especially in cooperation with IL-10 [90]. Another finding in this regard is that IL-4 production by T cells from remitting MS patients is higher than progressive MS patients [91].

IL-4 and IL-10 have adverse effects on IFN-gamma, hence it has been demonstrated that IL-10 changes the activity of macrophages and its role in Ag presenting, so they can decrease Th1 cytokines production [92]. IL-4 decreases IFN-gamma levels differently by suppression of cells that produce IFN-gamma in response to pathogens and also by improving Th2 differentiation. It has been observed that elevated levels of TGF beta as Th2 cytokines will be accompanied by improving conditions of EAE in mice and rats [93]. Detection of IL-10 mRNA was carried out in a survey on CNS of diseased animals and results demonstrated elevated IL-10 levels at the remission phase of the disease. It has been shown that inducing the immune system to produce IL-4 by some stimulation can have

ameliorating consequences in EAE [94]. However, another study observed that susceptibility to EAE in mice is independent of IL-4 production; therefore we cannot simply judge the role of IL-4 in the regulation of EAE. IL-4 and IL-10, based on the time of production, especially at first stage and reverse condition of disease, can stimulate the proliferation of Th2 clones and in this manner; they have an inhibitory role in EAE. Th2 cells regulation of EAE and inhibition of immune disease is possible by induction of Th2 cells, especially through cytokine production in response to auto-antigens [95]. There are some genetic methods for prevention or reversion of EAE by transduction of auto-reactive T cells with IL-10 and IL-4 genes which were placed in plasmids [96, 97].

TGF beta is another anti-inflammatory cytokine that has protecting effects against autoimmune diseases through inhibition of the immune system. TGF beta affects immunological disorders by changing and moderating the activity and proliferation of immune cells [98]. TGF beta can suppress many aspects of the immune system including cytokines and immune cells to affect the pathogenesis of neuro-immunological diseases, especially multiple sclerosis [99]. Results from studies on EAE have shown that TGF beta can inhibit relapsing in mice. The entrance of autoimmune T cells to CNS via blood-brain barrier can be inhibited by TGF beta. It also affects pathways of cytokine production and mostly suppresses the production of pro-inflammatory cytokines, and cytokines that are released in response to adhesion molecules stimulations. Some interesting studies have been done on the possible role of TGF beta in decreasing duration of acute and relapsing EAE by inhibiting TGF beta with antibodies and results from these studies showed that elevated levels of TGF beta can be considered as a factor that reduces susceptibility to MS [100].

IL-4, IL-10, and IL-13 are some Th2-type cytokines, which have adverse effects on Th1-type responses, especially Th1-type cytokines [101]. Currently, few studies have been done to determine the aspects of acute or chronic alcohol consumption, which can affect Th2-type cytokines. Chronic alcohol consumption can reduce inflammatory cytokines production such as IFN-gamma and this condition is appropriate for Th2-type cytokines to be dominant.

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Table 1. Effect of alcohol on different immune cells and MS

Cell type	Effect
Lymphocytes	decreased the size and cell number of lymphocyte (T cell) in the thymus, spleen, and lymph nodes [21, 22]
NK cell	reduction of the amount and activity of large granular lymphocyte/NK cells, suppress the activity of NK cells [51]
APCs	Impaired delayed-type hypersensitivity response, decrease in monocyte antigen-presenting cell function [55]
DC	inhibited monocyte-derived myeloid dendritic cell capacity [106]
Cytokines	Inflammatory reduces IFN-gamma levels [75]
	Auto-inflammatory increase in IL-10 levels, release TGF beta (inhibiting T cell proliferation and decreasing cytokine production in monocytes) [103]

Table 2. Effects of acute and chronic alcohol consumption on immune cells

Cell	Acute alcohol consumption	Chronic alcohol consumption
Monocyte	Increasing of IL-10 Decreasing of IL-6, IL-12, TNF α , and effercytosis [54]	Increasing TNF- α , IL-6 and phagocytic activity [56]
Dendritic cell	-	Increasing of IL-10 [57] Decreasing of IL-12 and CD80/CD86
T lymphocyte	Increasing of apoptosis [39]	Increasing of IL-2, IL-4, IL-10, vaccine response, and memory T cell Decreasing of IFN- γ , IFN- γ /IL-10 ratio, Naïve T cell, and antigen-specific responses [41]
B lymphocyte	Increasing of apoptosis and IgA [44]	Increasing of IgA and IgM [44]

IL-10 is produced by Th2 cells and has different effects on humoral and cellular immune responses. IL-10 strengthens humoral immune responses but it suppresses many aspects of cellular immune reactions such as inflammatory responses and Th1 cytokines and antigen-specific T cell amounts [102]. An increase in IL-10 levels in vitro, which is produced by monocyte in response to bacterial stimulation, is another effect of acute alcohol consumption. TGF beta is also an anti-inflammatory cytokine which can reduce immune system responses to inflammation and antigen-specific T cell count. Monocytes release TGF beta especially in response to bacteria in-vitro and elevated alcohol levels, which similar to physiological constriction can increase TGF beta production [103]. Improving Th2-type immune responses, inhibiting T cell proliferation and decreasing cytokine production in monocytes are some effects of elevated TGF beta level in response to alcohol consumption.

Other beverages

Although alcoholic beverages can have harmful effects on the immune system, there are other groups of beverages that can protect immune cells against damages; since they have antioxidants components. It has been shown that exposure to alcohol as ethanol in mice causes a decrease in baseline cell number. Significant variations have not been observed in baseline cell numbers between mice in case and control group that consume alcohol like wine and water, respectively. There are, however, differences in lymphocyte response to lipopolysaccharide between mice consuming alcohol and mice consuming alcohol as wine due to the fact that ethanol has inhibitory effects on lymphocyte response [104, 105] (**Tables 1 and 2**).

Conclusion

MS is an autoimmune disease, in which autoreactive T cells and B cells and inflammatory cytokines are involved. Therefore many therapies for multiple sclerosis disease are based on reducing inflammation and suppressing the immune system. Acute and moderate alcohol consumption suppresses the general condition of the immune system and its responses to pathogens. Chronic alcohol consumption also suppresses the general condition of the immune system, but increases immune respons-

es to the pathogens. Unfortunately, we are unable to recommend any therapeutic dosage or frequencies of alcohol use for immune system suppression due to lack of pieces of evidence. We suggest that more studies on large populations should be performed. We also believe that search for alternatives of alcohol with much less side effects should be performed. So in most cases, alcohol consumption has an inhibitory effect on immune responses and this effect needs further studies to take into consideration as a therapeutic factor.

Disclosure of conflict of interest

None.

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