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Smoking and disability progression in multiple sclerosis

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1. Introduction

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system, characterized by localized areas of inflammation, demyelination, and axonal loss. It is widely accepted that susceptibility to the disease depends on a combination of genetic and environmental factors and their interactions. Smoking is one of the risk factors for the development of MS that has also been suggested to adversely influence the severity and progression of the disease.

2. Clinical studies

The majority of studies exploring the association between smoking and MS severity and progression have detected a significant relationship. However, a variety of methods and outcome measures have been used, making it difficult to draw conclusions across studies. Several studies have observed increased Expanded Disability Status Scale (EDSS) scores and Multiple Sclerosis Severity Score (MSSS) among smokers compared to nonsmokers [1]. Smoking has been associated with the rate of conversion from relapsing remitting to secondary progressive disease, and with time from MS onset to fixed disability milestones as measured by EDSS [1]. The association is supported by the presence of a dose-response effect of smoking on disability in terms of EDSS and MSSS changes [2]. Continued smoking after MS diagnosis has consistently been associated with faster disease progression [3,4]. Each additional year of smoking after the diagnosis has been estimated to accelerate the time to conversion by 4.7% [4]. Smoking has also been associated with magnetic resonance imaging (MRI) markers of disease progression such as increased T2-weighted lesion volume and greater brain atrophy [1]. Furthermore, smoking may affect the efficacy of disease-modifying drugs, and contribute to the induction of antidrug antibodies to biological therapies, which may abrogate the therapeutic effect of the treatment [5].

A hospital based cohort including a large proportion of patients with primary progressive MS found no evidence suggesting that smoking influences disease progression [6]. In this study, data on smoking history was collected over 20 years after the first patient was included into the database and a substantial proportion of the patients could not complete the smoking questionnaire, which may have introduced bias.

A Norwegian study used cotinine as a marker of tobacco use, and found no association between cotinine levels and disease activity or progression [7]. However, the levels of cotinine are also high in users of smokeless tobacco, and nicotine, when considered in isolation of the products of combustion, has been shown to reduce MS risk and ameliorate the severity of experimental autoimmune encephalomyelitis [8]. In the Norwegian population, there are as many daily snuff users as there are daily smokers, and cotinine levels may not be a good proxy for smoking in this population.

Studies exploring a potential impact of smoking on disease progression in patients with clinically isolated syndrome have been more conflicting. Generally, studies using self-reported smoking habits have detected an association between smoking and disease progression, whereas cotinine levels have not correlated well with disease progression in studies using cotinine as a measure of tobacco consumption [1].

A cross-sectional survey of 1372 MS patients found that smoking increased the risk of reaching EDSS 6 in the relapsing onset group, but not in the progressive onset group [9]. Similarly, in a study of patients with primary progressive MS, no association was found between smoking and disease progression [10]. These findings indicate that smoking may primarily be associated with the inflammatory mechanisms that influence disease progression during the relapsing remitting phase and the transition from relapsing remitting to secondary progressive disease, whereas the impact of smoking on the diffuse process of axonal degeneration in primary progressive MS appears to be less clear. Different mechanisms may thus underlie disability progression in relapsing remitting MS and progressive MS.

3. Potential biological pathways

The biological mechanisms by which smoking could affect the susceptibility to and progression of MS are unclear. However, several hypotheses have been put forward to explain why smoking may affect MS progression. These include direct toxicity to neural tissue and direct or indirect modulation of immune responses.

Smoking contains high concentrations of free radicals such as nitric oxide, hydrogen cyanide, and carbon monoxide. Oxidative
stress has been suggested to correlate with increased disability in patients with MS. Nitric oxide has been associated with axonal degeneration, predominantly in physiologically active or demyelinated axons [11]. Elevated levels of nitric oxide metabolites in the cerebrospinal fluid have been found to correlate with the volume of gadolinium-enhanced lesions on MRI [12]. Furthermore, nitric oxide is a powerful vasodilator increasing vascular permeability which may contribute to compromising the integrity of the blood brain barrier. Chronic cyanide exposure and carbon oxide result in widespread cerebral demyelination in animal models of MS [13].

Smokers have been reported to have lower levels of plasma uric acid, the most abundant aqueous antioxidant, possibly due to smoking being a significant source of oxidative stress [14]. Uric acid levels have been inversely associated with MS severity and progression [15].

Exposure to tobacco smoke modulates both innate and adaptive immune cells, and induces a sustained, long-term inflammatory response, immune suppression, alteration of cytokine balance, and epigenetic modifications. Smokers have increased levels of inflammatory markers and endothelial adhesion molecules which may facilitate migration of immune cells into the CNS [16].

It is not clear if the worse disease progression observed in smokers is purely due to the biological influence of smoking on the disease, or if other underlying factors, associated with smoking, are involved. A dual effect of smoking on alveolar macrophages has been observed, with enhancement of both chronic inflammation and susceptibility to infections. To some degree, smoking could be linked to MS by increasing the frequency and persistence of respiratory infections. The risk of MS exacerbations has been reported to be higher during respiratory infections, and the exacerbations lead to more sustained neurological damage if they occur at the time of a clinical infection [17].

Smokers are more likely to suffer from cardiovascular disorders, which have been found to increase the risk of MS development and progression [18]. It has been suggested that cardiovascular comorbidities might increase disease progression by increasing peripheral inflammation, which in turn may activate the systemic inflammatory response and worsen inflammatory demyelination and neurodegeneration in MS [19]. The Framingham Risk Score, a gender-specific algorithm used to estimate the 10-year risk of developing cardiovascular disease, has been associated with MS severity and progression [20]. Presence of two or more cardiovascular risk factors could thus act in concert to increase disability in MS patients. Smokers with MS are also more likely to suffer from comorbid autoimmune diseases [21]. Although there is accumulating evidence that suggest a pathophysiological role of smoking on MS disease progression, it is also possible that comorbidities contribute to the increased disability progression among patients who smoke.

Another mechanism by which smoking may affect MS progression is by inducing gastric and intestinal microbiome alterations. The microbiome affects the immune system by regulating the colonic mucosal barrier and intestinal lymphoid tissue, and by inhibiting pathogenic microorganisms and modulating inflammatory responses [22]. Although increasing evidence suggest a critical role of the gut microbiota in MS development and progression, more research is needed to better understand how smoke-induced changes in the gut microbiome affect neuroinflammation.

There is evidence suggesting that epigenetic modifications may explain the link between smoking and inflammatory responses. Smoking induces epigenetic alterations, including DNA methylation, histone modifications, and non-coding RNA sequences, that may lead to stable but reversible changes in gene expression. Several loci have been identified where methylation levels associate with smoking intensity and time from cessation [23-24]. Epigenetic modifications may lead to increased expression of multiple inflammatory genes, which may act in concert with other smoke-related molecular mechanisms to influence MS disease progression, such as oxidative stress.

4. Clinical implications and future perspectives

The majority of clinical studies investigating the influence of smoking on disease progression have shown an adverse effect of smoking on MS disease severity and progression, and smoking may also reduce the efficacy of disease-modifying drugs, which has important clinical implications. Based on current knowledge, smoking should be considered a modifiable risk factor for MS progression and patients with MS should be strongly encouraged to stop smoking. Smoking cessation also has several other health benefits in terms of reduced morbidity and mortality.

More prospective studies are needed to reach a solid consensus with regard to all effects of smoking on the disease course of patients with MS. The influence of smoking on disease progression in different genetic contexts and the role of smoke-induced epigenetic modifications on disease progression should be explored. Further work to elucidate the mechanisms underlying the association between smoking and MS progression may provide additional insights into the pathogenesis of MS.

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Declaration of Interest

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Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

an important review about the outcomes of smoking in patients with MS.


a comprehensive review about the impact of smoking on the immune system


a comprehensive review about smoking-induced epigenetic alterations.