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Review article

Vascular comorbidities in the onset and progression of multiple sclerosis

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ABSTRACT

Vascular comorbidities are common in the general population and are associated with adverse health outcomes. In people with multiple sclerosis (MS), an increasing amount of evidence suggests that vascular comorbidities are also common, but an association with MS risk and disability has not been conclusively established. This review aims to critically examine published data on the relationship between vascular comorbidities (including vascular risk factors) and MS. The evidence suggests an increased risk of MS in people with a high BMI during childhood or adolescence but not adulthood. People with established MS appear to have a slightly increased risk of cardiovascular disease and a greater proportion of people with MS die from cardiovascular disease, which has important implications for clinicians trying to identify risk factors for cardiovascular disease and reviewing treatment options. In relation to whether vascular comorbidities influence MS clinical disability or other aspects of the disease course, the key finding was that having type-2-diabetes, hypertension, dyslipidaemia or peripheral vascular disease at any point in the disease course may be associated with a greater progression in disability. Additionally, a negative effect of high cholesterol and triglycerides and a positive effect of higher HDL (high density lipoprotein) levels on acute inflammatory activity were observed on magnetic resonance imaging. The results of the published clinical trials of statins as an intervention in MS were however conflicting and care needs to be taken when treating people with MS with statins. Taken together, the literature seems to indicate a potential association of vascular comorbidities with MS risk and disability, but the number of prospective studies was sparse, thus precluding ascription of causality. We therefore recommend that future studies of the frequency and effects of vascular comorbidities on MS risk and disability should be prospective and objective where relevant.

Contents

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1. Introduction

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) with autoimmune, inflammatory and neurodegenerative components which may influence each other or alternatively may have independent natural histories. Although the typical age of onset of MS is in the third and fourth decades of life, the burden of disease is most marked in the fifth to seventh decades [1]. MS affects more than 2.5 million individuals worldwide [2], with higher incidence and prevalence in women than men [3]. MS has a highly variable inter and intra-personal clinical course, both in pattern and rate of deterioration [1].

In relation to aetiology, MS is a complex disease in which multiple environmental and lifestyle risk factors act together in a genetically susceptible individual to cause the disease [4]. Environmental and lifestyle risk factors include low sunlight exposure and vitamin D, cigarette smoking and exposure to Epstein–Barr virus [3–5]. However it is not entirely clear whether the same factors also modulate disease progression and whether the putative factors that modulate the inflammatory components of the disease are the same as those that potentially modulate the neurodegenerative components. In the last several years, vascular risk factors and vascular comorbidities such as obesity, dyslipidaemia, type-2 diabetes and cardiovascular disease have been associated with MS onset and disease progression [4,6]. In line with this background, MS has been proposed to have, in part, a vascular basis due to its shared pathophysiology with these comorbidities, including endothelial dysfunction [7], inflammation [8], and cardiovascular autonomic dysfunction [9].

In this review, we examine the current literature on the relationship between cardiovascular risk factors including obesity, hypertension, dyslipidaemia, type-2 diabetes, and cardiovascular disease with MS risk, disability progression and mortality. Throughout the text, the term vascular comorbidity refers to cardiovascular risk factors and diseases.

2. Obesity and MS

2.1. Prevalence of obesity in people with MS and comparison with healthy populations

The prevalence of obesity in people with MS has been investigated in several studies. For example, in a large study of persons with MS ($n = 8983$), 31.3% of participants were classified as overweight and 25% as obese [10]. A study of 123 women with MS from Oregon found 47.5% of participants to be overweight and 25.8% were obese [11]. In a study of by Pilutti and colleagues [12], 36.3% of the 168 MS patients were overweight and 32.7% were obese. In a 24-month longitudinal study of 269 individuals with relapsing–remitting MS (RRMS), 24.0% and 28.3% were classified as overweight and obese respectively [13]. Similarly, a study by Marrie and colleagues [14] reported that nearly half had high BMI at MS onset, with 26.4% being overweight and 23.8% being obese.

A number of studies compared the prevalence of high BMI to a control population. A study by Khurana and colleagues [15] found that 4339 veterans with MS had a slightly higher age and sex-adjusted prevalence of overweight than veterans in general (42.3% vs. 39.6%, respectively) but a lower adjusted prevalence of obesity (20.1% vs. 33.1%). In contrast, other case–control studies were not able to detect any difference in BMI between MS cases and controls, though these studies were relatively small (sample size ranging from 16 to 68) compared to that of Khurana and colleagues [16–18]. Two other studies even reported a lower BMI in MS cases than controls [16,19]. Overall, there is currently no evidence that the prevalence of overweight and obesity in MS is higher than that of the general population. The use of self-reported height and weight may have led to underestimation of overweight and obesity in these investigations.

2.2. Obesity and MS risk

Table 1 provides an overview of the studies that have examined the association between BMI and MS risk. It shows that a number of prospective and case–control studies have observed an association between BMI in childhood [20,21] and adolescence [22,23] and MS risk; however no associations have been found between BMI in adulthood and MS risk [22,23]. Interestingly, the two studies that examined childhood BMI both found that the association was only present in females and not in males, both showing a clear dose-dependent relationship between childhood BMI in females and subsequent MS risk [20,21]. In addition, two studies found a dose–response relationship between BMI and MS when BMI was measured at ages 18 and 20 [22,23] but no association was observed when BMI was measured in adulthood [22,23]. Certainly having an association with exposure prior to disease onset is potentially supportive of a causal directionality, but it is interesting and perhaps disruptive to a causal interpretation that the BMI–MS association does not track forward to later adulthood. It may be that by this age other factors that occur among all adults in their later decades of life nullify any appreciable differences in BMI between MS cases and other adults.

A substantial limitation of these studies was the fact that they were unable to adjust for sun exposure and/or 25-hydroxyvitamin D serum levels. It is well known that individuals with high BMI have less sun exposure and lower vitamin D levels [24,25]. In part, this may be due to changes in behaviour and the effects of increased adiposity on systemic vitamin D availability. Low sun exposure and vitamin D levels are now established risk factors for MS. [26–28] It is therefore feasible that the observed associations between childhood/adolescence BMI and MS may be explained by the fact that cases had less sun exposure and lower serum vitamin D levels. That said, there are a number of deleterious effects of obesity that might independently contribute to MS risk, such as increased oxidation and dyslipidaemia, so both BMI and sun/vitamin D are worthy covariates to assess in studies of MS risk and disability progression. Importantly, the absence of association between adult BMI and the risk of MS is interesting and

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