



Cardiovascular Autonomic Dysfunction and Falls in People With Multiple Sclerosis: Is There a Link? An Opinion Article

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INTRODUCTION

Falls and fall-related injuries are highly prevalent in people living with multiple sclerosis (MS). A multinational meta-analysis revealed that 56% of people with MS (pwMS) fall at least once in any 3-month period (Nilsagård et al., 2015) and 11–42% of falls are injurious (Gunn et al., 2014; Mazumder et al., 2014). Falls are of clinical concern as they increase the burden of morbidity and mortality (Grossman et al., 2018). Mobility impairments, progressive MS, and cognitive impairment are the most commonly reported risk factors for falls in this clinical population (Gunn et al., 2013; Gianni et al., 2014; Sosnoff and Sung, 2015).

Despite the recent progress in disease-modifying medical treatments, as well as the numerous randomized controlled trials aiming to reduce falls, the evidence regarding effectiveness of interventions for fall-prevention in MS remains inconclusive (Hayes et al., 2019). Although such inconclusiveness is potentially related to the lack of methodological quality of intervention studies, it also highlights the need for accurate characterization of fall-etiology in this patient population. The success of fall-prevention programs is often based on their ability to effectively target underlying physiologic conditions. Therefore, in order to correctly prioritize rehabilitation strategies in MS, it is essential to identify all modifiable or partially-modifiable risk factors for falls.

Multiple sclerosis (MS) is characterized by damage to the central nervous system (CNS) as a result of inflammatory demyelination and neurodegeneration (Ghasemi et al., 2017). While such damage often translates into impairments of cognition and motor function, which are reasonably recognized as the main determinants of falls (Gunn et al., 2013), a growing body of research has explored the relationship between MS-related CNS damage and autonomic dysfunction (Racosta et al., 2015; Findling et al., 2020). Autonomic dysfunction can severely impact the quality of life in pwMS and often affects multiple organs and systems including the bladder, bowels, heart, as well as sexual and sudomotor functions (McDougall and McLeod, 2003; Lensch and Jost, 2011). A meta-analysis has concluded that cardiovascular autonomic dysfunction (CAD) is highly prevalent, with 19–42% of pwMS affected by this condition (Racosta et al., 2015). Importantly, CAD is one of the main drivers of orthostatic hypotension (OH) and contributes to symptoms of orthostatic intolerance, such as dizziness, which

can directly or indirectly increase the risk of falling (Magkas et al., 2019). In this article, we aimed to outline the potential relationship between CAD and falls in pwMS.

CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN MS

While pathophysiological processes of inflammation and neurodegeneration are thought to contribute to the development of CAD, the etiology of autonomic dysfunction in MS has not been elucidated (Findling et al., 2020). It has been postulated that CNS lesions, as assessed through magnetic resonance imaging, may be involved in the pathogenesis of CAD. For instance, several observational studies found that brainstem (Habek et al., 2016), midbrain (Saari et al., 2004), hippocampal (Winder et al., 2019), and spinal cord (de Seze et al., 2001) lesions were associated with indices of cardiovascular dysfunction including reduced heart rate variability (HRV) and increased blood pressure variability. However, due to conflicting evidence in the literature (Nasseri et al., 1999; Damla et al., 2018), it is not possible to make any conclusive statement as to whether CAD may be caused by CNS damage or by other epiphenomena of disrupted autonomic balance (Findling et al., 2020).

Common pharmacological treatments used in MS, such as immunotherapies, have also been linked to the development of CAD. Particularly, patients are often prescribed with Fingolimod, a sphingosine 1-phosphate receptor modulator (Chaudhry et al., 2017). Sustained usage of this immunomodulating drug has consistently been associated with impairments of cardiac autonomic function in pwMS. For instance, longitudinal studies have shown that prolonged treatment with Fingolimod significantly reduced both HRV and cardiovagal baroreflex sensitivity (BRS) (Racca et al., 2016; Simula et al., 2016; Vehoff et al., 2017). Additionally, administration of high dosage intravenous corticosteroids (e.g., methylprednisolone) and polypharmacy may also negatively affect cardiovascular autonomic function in MS (Vasheghani-Farahani et al., 2011; Findling et al., 2020).

The clinical implications of CAD in the context of MS are not clear. A large population-based cohort study revealed that, within 1 year of diagnosis, patients had an increased risk of stroke, myocardial infarction, and heart failure compared to the general population (Christiansen et al., 2010) and it was suggested that CAD may be involved in the etiological pathways of cardiovascular disease (Kaplan et al., 2015). Notably, the baroreflex plays a central role in buffering both the increases and decreases in blood pressures that normally occur in daily life (Kaufmann et al., 2020). Thus, baroreflex dysfunction represents a risk factor for both cardiovascular complications such as stroke and myocardial infarction (La Rovere et al., 2008; Lin et al., 2019), but also for conditions such as orthostatic dizziness, which is highly prevalent in pwMS (Habek et al., 2016).

Abbreviations: BP, blood pressure; BRS, baroreflex sensitivity; CAD, cardiovascular autonomic dysfunction; CNS, central nervous system; HR, heart rate; HRV, heart rate variability; OH, orthostatic hypotension; MS, multiple sclerosis; pwMS, people with multiple sclerosis.

RELATIONSHIP BETWEEN CAD AND FALLS

While there is growing evidence that CAD can manifest in OH or symptoms of orthostatic intolerance/dizziness due to baroreflex dysfunction in MS (Racosta et al., 2015), its relationship with falls has not received much scrutiny. Cross-sectional studies have consistently reported that, compared to age-matched healthy controls, pwMS have reduced HRV and baroreflex function (Tombul et al., 2011; Shirbani et al., 2018), both of which have been found to predict falls in patient populations characterized by dysautonomia (Castaldo et al., 2017; Razjouyan et al., 2017; Terroba-Chambi et al., 2020; Zanotto et al., 2020). A direct biological mechanism linking baroreflex dysfunction and falls can be reasonably theorized. Specifically, the impaired ability of baroreceptors to evoke tachycardia and vasoconstriction to effectively buffer a fall in blood pressure (BP) during an orthostatic challenge may lead to sudden onset of cerebral hypoperfusion (Kaufmann et al., 2020).

Orthostatic hypotension is a significant hypoperfusion-mediated risk factor for falls in the general geriatric population (Mol et al., 2019). In the context of MS, observational studies employing self-report or sphygmomanometer BP measurements have reported a high prevalence of OH or presyncope/syncope in middle-aged patients (36–38 years-old), ranging from 18–24% (Al-Araji et al., 2003; Kale et al., 2009). This is comparable to the prevalence (17.3%) found in much older populations (74 years-old) of community-dwelling adults (Cooke et al., 2013). Notably, even subtle alterations of BP response to orthostatic challenges (i.e., without a clear diagnosis of OH) can be predictive of falls (Shaw et al., 2015). Symptoms of orthostatic intolerance/postural dizziness are also highly prevalent (50–67%) in MS populations (both remitting-relapsing and progressive MS) (Flachenecker et al., 1999; Gunal et al., 2002; Al-Araji et al., 2003; Habek et al., 2016), which could be indicative of BP decrements during changes of body posture or prolonged standing.

Although falls caused by cerebral hypoperfusion are sometimes classified as syncopal events and therefore excluded from the operational definition of a fall, the etiology of falling is complex and often multifactorial (World Health Organization, 2008). Therefore, hypoperfusion symptoms such as dizziness may also act as secondary contributors to falls that are mainly precipitated by other factors such as sudden losses of balance or environmental hazards. International research collaboratives such as the ProFaNE group have recommended against excluding OH-related falls from the operational definition, as this would introduce a definitional artifact leading to biased findings (Lamb et al., 2005). Furthermore, the importance of recording fall-related circumstances has been emphasized (Hauer et al., 2006; Coote et al., 2014). In this regard, prospective cohort studies conducted in MS populations have often failed to report perceived causes of falling (Chinnadurai et al., 2018; Tajali et al., 2019), which limits the ability to identify precipitating factors. An observational study by Gunn et al. (2014) revealed that only 1.8% of recorded falls were directly attributed to dizziness/fainting, as opposed to a much greater proportion of falls that were precipitated by a loss of balance (19.4%) or legs

giving way (8.7%). However, participants could not describe the perceived cause for the great majority of falls experienced (49%) in this study. While this observation is most likely related to the multifactorial etiology of falling and recall-bias, it could be hypothesized that CAD may represent a “hidden” contributing factor due to the fact that unexplained falls are often attributed to factors such as OH (Finucane et al., 2017; van Wijnen et al., 2017), which can be asymptomatic (Freeman et al., 2020).

Fatigue-related processes, in addition to cerebral hypoperfusion, may underscore the mechanisms by which CAD leads to falls in MS. Several studies have focused on the relationship between autonomic impairments of cardiac function and fatigability in pwMS (Lebre et al., 2007; Krbot Skorić et al., 2019). Lebre et al. (2007) observed that patients with fatigue had lower BP response to handgrip testing compared to those who were fatigue-free (14.6 ± 9.1 mmHg vs. 21.7 ± 7.2 mmHg, $p < 0.05$), postulating that impaired sympathetic outflow to the heart and vasculature may be a significant driver of fatigue. Similarly, Krbot Skorić et al. (2019) found negative correlations between Valsalva ratio and the modified fatigue impact scale ($r = -0.306$, $p = 0.011$) in a cohort with early-stage MS, suggesting an association between autonomic nervous system impairment and MS-related fatigue. Such evidence remains scarce and confounded by methodological design issues (e.g., a causative relationship cannot be inferred). However, a review by Sternberg (2017) has suggested that impaired neurovisceral integration of cardiovascular modulation, manifesting through the dysregulation of both sympathetic and parasympathetic responses, is involved in the etiology of multiple MS-related symptoms including fatigue. Additionally, CAD may contribute not only to physical but also cognitive fatigue in MS (Sander et al., 2017), as significant associations between cognitive decline and objective physiological markers of CAD such as reduced HRV (Sander et al., 2019) or blunted BP response to sustained handgrip testing (Niepel et al., 2013) have been highlighted. More importantly, prospective cohort studies of both healthy and neurological populations have suggested that OH arising from baroreflex and sympathetic dysfunction could lead to cognitive deterioration (e.g., through white matter lesions) as a result of chronic hypoperfusion and suboptimal cerebral autoregulation (Dadar et al., 2020; Zimmermann et al., 2020). Therefore, impairments of cognitive function, which are recognized as a risk factor for falls (Gunn et al., 2013; Sosnoff et al., 2013), may represent a further mediator of the relationship between CAD and fall-risk. It has been proposed that parasympathetic overactivity arising from inflammation-induced vagal activation would cause reductions in BP and orthostatic intolerance with concomitant impaired ability to maintain mental focus (Sander et al., 2017). In turn, cognitive impairment and/or fatigability

can increase the risk of falling by impairing attention and the ability to evaluate intrinsic or extrinsic hazards during walking (Segev-Jacobovski et al., 2011).

Lastly, CAD seems to be more common among people affected by primary progressive MS (Findling et al., 2020), who tend to experience more falls compared to people with other subtypes of MS (Nilsagård et al., 2015). While this higher risk of falling is certainly related to greater overall disability (Penner et al., 2020), it is also plausible that autonomic impairments leading to orthostatic dysregulation of BP and/or fatigue may play a role in the higher occurrence of falls in progressive MS populations.

FINAL CONSIDERATIONS

In this opinion article, we discussed the potential relationship between CAD and falls in people with MS. To the best of our knowledge, there is currently no information as to what proportion of patients suffering from falls is also affected by CAD. Although some preliminary evidence seems to indirectly point toward the existence of a mechanistic link between pathological alterations of cardiovascular autonomic function and falls in this clinical population, observational studies designed to explore this research hypothesis have yet to be conducted. Studies investigating purported physiological mechanisms of CAD, such as baroreflex dysfunction, in relation to signs and symptoms of orthostatic intolerance and falls would be a logical next step toward a better understanding of fall-etiology in MS. This research would have translational impact on rehabilitation strategies for fall-prevention if a significant relationship between CAD and falls was to emerge. Specifically, personalized pharmacologic/non-pharmacologic interventions targeting the underlying autonomic impairment may be considered as part of a more comprehensive fall-prevention strategy.

AUTHOR CONTRIBUTIONS

TZ drafted the original manuscript. MH, CM, KW, and JS critically revised the manuscript. All authors agree to be accountable for the content of the work.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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