Multiple Sclerosis and the Cardiovascular System: an overview from cardiovascular risk and clinical characteristics to treatment

Esclerose múltipla e o sistema cardiovascular: uma visão geral do risco cardiovascular e das características clínicas até o tratamento

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ABSTRACT

Objective: Review the relationship between Multiple Sclerosis (MS) and the cardiovascular (CV) system, as well as the CV manifestations of the disease and the CV complications of treatment.
Methods: We performed a non-systematic review of the main databases, with no time limit.
Results: People with MS tend to have a different CV risk than the general population, with a higher prevalence of hypertension, hyperlipidemia, overweight, ischemic heart disease, and peripheral and cerebral artery disease. In addition, cardiac alterations can be present in any part of MS patient care. Furthermore, MS treatments are not innocuous for the CV system and require attention, especially considering fingolimod and mitoxantrone.
Discussion: The findings could partially explain the higher mortality rates found in this population. Furthermore, at the onset, dysautonomia symptoms, like postural orthostatic tachycardia syndrome, can be used as a clinical marker of patients at higher risk to evolve from clinically isolated syndrome to MS. Finally, MS not only progress badly when associated with CV risk factors but are also at increased risk of CV morbidity and mortality.
Conclusion: Physicians addressing MS patients should be aware of their increased cardiovascular risk and the impact that adequate control of these factors can have on disease progression, patient lifespan, and global care.

Keywords: Multiple Sclerosis; Central Nervous System Diseases; Cardiovascular Diseases; Heart Disease Risk Factors; Demyelinating Diseases

RESUMO

Objetivo: Analisar a relação entre a esclerose múltipla (EM) e o sistema cardiovascular (CV), bem como as manifestações CV da doença e as complicações CV do tratamento.
Métodos: Foi realizada uma revisão não sistemática das principais bases de dados, sem limite de tempo.
Resultados: Pessoas com EM tendem a ter um risco CV diferente da população em geral, com maior prevalência de hipertensão, hiperlipidemia, sobrepeso, cardiopatia isquêmica e doença arterial periférica e cerebral. Além disso, as alterações cardíacas podem estar presentes em qualquer parte do tratamento do paciente com EM. Além disso, os tratamentos da EM não são inócuos para o sistema CV e requerem atenção, especialmente considerando o fingolimod e a mitoxantrona.
Discussão: Os achados podem explicar parcialmente as taxas de mortalidade mais altas encontradas nessa população. Além disso, no início, os sintomas de disautonomia, como a síndrome de taquicardia postural ortostática, podem ser usados como um marcador clínico de pacientes com maior risco de evoluir da síndrome clinicamente isolada para a EM. Por fim, a EM não só progride mal quando associada a fatores de risco CV, mas também apresenta um risco maior de morbidade e mortalidade CV.
Conclusão: Os médicos que lidam com pacientes com EM devem estar cientes de seu risco cardiovascular aumentado e do impacto que um controle adequado desses fatores pode ter na progressão da doença, no tempo de vida do paciente e nos cuidados globais.

Palavras-chave: Esclerose múltipla; Doenças do Sistema Nervoso Central; Doenças cardiovasculares; Fatores de Risco de Doenças Cardíacas; Doenças Desmielinizantes

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INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disorder, with an autoimmune mechanism which leads to progressive disability in the patient. Its development is linked to exogenous, genetic, and environmental factors[1]. Some studies are showing the correlation between this progression and systemic diseases that increase cardiovascular (CV) risk, leading to a relevant incidence of negative outcomes for those patients[2]. In this paper we will explore CV risk factors in MS and how they contribute to higher mortality and worse disease outcomes for MS patients; furthermore, we will address CV manifestations and findings in MS patients; and discuss CV risks and complications regarding drugs used in MS management.

METHODS

We conducted a non-systematic review of the relationship between MS and the CV system. No time restrictions were applied to the literature.

RESULTS

Relationship between Cardiovascular risk and Multiple Sclerosis

People with MS tend to have a different cardiovascular risk than that of the general population. The MS population is associated with a higher prevalence of hypertension, hyperlipidemia, and being overweight. Risk manifestations may include coronary artery disease, cerebrovascular disease, and other major cardiovascular events[3-6] .

These risk factors are associated with vascular atherosclerosis, which can lead to brain atrophy and which, in turn, is increased by MS intrinsic disease activity[7,8] . Patients with MS associated with hypertension and heart disease have been shown to present a decrease in gray matter and cortical volumes; patients with MS that are smokers were also associated with a decrease in total brain volume[3,4] .

This higher CV risk in MS patients could partially explain the higher mortality rates found in this population. One study found a 7-year shorter life expectancy and an almost three-fold mortality rate in MS patients compared to the general population[9,10] . Another study found a higher risk of MS patients developing stroke compared to the general population[11].

Despite these data, there are relatively few population-based studies (North America and Scandinavia) that evaluated the epidemiology of comorbid vascular disease in MS. Based on these studies, the prevalence of ischemic heart disease was less than 5%; however, the prevalence of these conditions increased with age[12].

The CV dysfunction found is probably multifactorial due to aspects such as autonomic nervous dysfunction, greater oxidative stress, and more systemic inflammation, in addition to physical disability. Injuries and disease progression can be associated with ischemic heart disease and peripheral and cerebral artery disease[3–6,13] . Another factor influencing the increased risk of CV disease in these patients is the fact that there is evidence of abnormal platelet activity. Studies show an increase in P-selectin expression, activation of the GP IIb / IIIa complex, and formation of platelet microparticles and platelet aggregates[14].

A study that evaluated 251 individuals with MS demonstrated that the higher the cardiovascular risk, the greater the risk of disability, relapses, and an increase in therapeutic methods. Using the Framingham risk score, which includes factors such as age, sex, systolic blood pressure, smoking, diabetes, and BMI, a survey analyzed the risk percentage of developing cerebral, coronary, and peripheral arterial disease, in addition to heart failure, in 10 years. For each score added to the Framingham risk scale, a 40% higher relapse rate and 60% higher risk of medication escalation was observed[7]. Thus, the increased CV risk found in MS, estimated through the Framingham CV Risk Score, was associated with significant disability and disease progression[9]. In other diseases, brain degeneration is also present, but in MS there is a chronic inflammatory pathology, which aggravates the case, with brain tissue damage in the spinal cord, and accumulation of iron in oligodendrocytes, myelin, and in the perivascular space. Inflammatory cells consume a lot of oxygen, and since perivascular infiltrated areas have a large amount of oxygen, the invasion can cause a decrease in oxygen tension, which may be below a critical limit level, affecting areas that already have low oxygen content in the brain and spinal cord. This could explain MS patients' higher sensitivity to CV risk, as assessed through the Framingham score[15].

Cardiovascular manifestations of Multiple Sclerosis

CV manifestations can be part of MS presentation. Autonomic dysfunctions, for example, appear in different ways in MS. Parasympathetic dysfunction is linked to MS progression and disability, while sympathetic dysfunction is associated with inflammation and clinical MS activity, and may also have a pathogenic role in the development of MS[16].

Patients with MS may develop autonomic dysfunction even at the onset of the disease. More than 2/3 of patients will develop signs and symptoms of autonomic dysfunction in the course of the disease. This interaction occurs mainly with the regulation of heart rate and ventricular repolarization[17]. Another study, which evaluated cardiovascular autonomic dysfunction, showed a decrease in heart rate variability in patients with MS[18].

Cardiac dysfunction can be present as well. A study that evaluated cardiac function in patients with MS found that they have decreased left and right ventricular systolic function. Moreover, in comparison with the controls, decreased diastolic and left atrial functions were also found[19,20] . In contrast, endothelial and arterial functions were preserved, as well as heart rate, which did not differ between the control group and patients with MS.

An interesting point about CV manifestations in MS is that postural orthostatic tachycardia syndrome (POTS) can be a predictor of conversion to MS in patients with clinically isolated syndrome (CIS), and is considered prevalent in patients with MS (19%) when compared to patients with symptoms of orthostatic intolerance without neurological impairment (10%)[21,22] .

Sympathetic denervation and central causes, such as sympathetic overdrive, hypovolemia, and involvement of the renin-angiotensin-aldosterone system are possible mechanisms that explain the correlation of POTS with MS. There are also autoimmune-based conditions that are relevant in this correlation - previous viral infections, after papillomavirus vaccination (HPV), and the presence of acetylcholine ganglionic anti-receptors[21,23,24] .

Other situations that may be present in MS are Takotsubo cardiomyopathy and rare cases of Brugada syndrome16. Moreover, a sympathetic and parasympathetic tone imbalance (hyperfunction of the parasympathetic tone) may reveal the Brugada pattern in an ECG, supporting the theory that autonomic nervous dysfunction is a possible culprit in this case[25,26]. In Takotsubo cardiomyopathy, due to the high adrenergic discharge, a worse outcome can be reached generating, for example, malignant ventricular arrhythmias. Takotsubo cardiomyopathy is a form of reversible myocardial dysfunction associated with emotional and physical variables. In patients with MS, this cardiomyopathy may represent an acute impairment of the cardiovascular center in the brain stem, and this acute-onset ventricular dysfunction syndrome in the absence of obstructive coronary artery disease has been related to patients with MS in the context of demyelinating plaques in the brain stem[27–29] .

Another cardiac alteration in MS patients is the occurrence of electrocardiogram abnormalities. Studies have shown a longer duration of the P wave and its dispersion in patients with MS compared to controls[30]. Some authors have reported an increased risk for atrial fibrillation, a sympathetic overexcitation mediated through the insular cortex. Another study also analyzed that MS is associated with prolonged cardiac repolarization. Other findings include alterations in the QT interval, reflecting abnormal time for repolarization[17,31] . Cardiac repolarization is regulated by the autonomic nervous system (especially related to sympathetic stimulation), and its deregulation can be a cause of life-threatening arrhythmias. Thus, the unfavorable CV results of the disease may also be related to the deterioration of the nervous system. Even though a prolonged QT interval cannot be considered an isolated marker of SNA function, it is mainly identified in the clinical evolution of the motor form of the disease, especially associated with spinal cord atrophy, secondary to axonal loss, and insula damage[31–33] .

Multiple Sclerosis treatments and Cardiovascular risks and complications

At present, there is no prophylactic therapy or curative treatment for MS. Thus, the objective of pharmacological and non-pharmacological practices is to reduce relapses and sequelae of the disease, preventing disabilities while also preventing any noticeable adverse effects. The course of MS can be changed by disease-modifying therapies (DMT), which modulate and suppress immune functions. They can regulate anti-inflammatory activity primarily in the relapsing phase of MS, reducing the rate of relapses and improving disabilities. Many experts recommend the use of DMT early in the disease to minimize later disabilities[34]. As it is known, MS can cause cardiovascular dysfunction in some patients and, in addition, some treatments can also contribute negatively to this condition, potentially leading to death[35].

One of the most discussed DMT is fingolimod, which was the first oral therapy approved for relapsing-remitting MS. Fingolimod is a sphingosine-1-phosphate receptor inhibitor that prevents lymphocyte egress from secondary lymphoid organs, protecting the central nervous system from infiltration of autoreactive lymphocytes[34]. One of the adverse cardiac side effects is AV block and bradycardia, especially soon after the therapy is initiated, which is why it is recommended to keep all patients under observation for 6 hours, always monitoring them with electrocardiograms[34,35] . The European Union specifies that all patients receiving their first dose of fingolimod should undergo a 12-lead ECG and have their blood pressure measured over 6 hours, measuring signs and symptoms of bradycardia and AV blocks[36]. This adverse event happens because three of the five known S1P are present in the cardiovascular system, and when fingolimod binds to these receptors in the atrial myocytes, potassium channels are activated, which leads to reduced electrical excitability and a decreased firing rate, causing bradycardia or AV conduction block[35]. However, understanding the potential interactions of fingolimod and the human body may add novel safety information for the treatment[36]. In 2017, the safety of fingolimod was validated through a first analysis in a START study, which observed over 4,000 patients treated with the drug. In this study, bradycardia and advanced AV blocks were seen in as low as 0.8% and 1.6%, respectively, of the whole population[37].

Another DMT used in the last decade for MS is mitoxantrone, which is a synthetic anthracenedione derivative used as an immunomodulatory agent, although its exact immunomodulation mechanism is not well understood yet. This drug has potential cardiotoxic effects

and some oncologists have already reported drug-related congestive heart failure in 2.6% to 6.0% of patients to whom cumulative doses of up to 140 mg/m² of mitoxantrone were administered in the treatment of leukemia or solid tumors[35]. A 2018 report from the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology described new evidence showing a high risk of cardiomyopathy, such that clinicians should not prescribe this drug to MS patients unless the potential therapeutic benefits greatly outweigh the risks[38].

A new and frequently used DMT for MS is rituximab, which is a chimeric anti-CD20 monoclonal antibody[34]. This drug targets the CD20 antigen based on the surface of mature B lymphocytes, causing selective transient depletion of CD20 B-cell subpopulations. This mechanism influences and regulates the immune response and can also help in cases of heart failure, demonstrating a meaningful improvement in LVEF, LV end-diastolic diameter, NYHA class, or N-terminal pro-B-type natriuretic peptide. Nevertheless, there is emerging data reporting that rituximab and other monoclonal antibody-based chemotherapy represent a newer class of medications that have cardiotoxic potential, as these DMT can also cause hypotension, hypoxia, acute myocardial infarction, arrhythmias, and cardiogenic shock during the infusion process[39].

Ozanimod is a recently approved selective sphingosine-1-phosphate receptor modulator that was also shown to be effective in relapsing-remitting MS[34]. The safety and tolerability of this drug was thus studied. Results showed that cardiac adverse events of special interest, prespecified based on clinical trial results with fingolimod, were similar for ozanimod and placebo, demonstrating no apparent safety issues[40].

Another drug used to treat patients with relapsing-remitting MS is dimethyl fumarate. This DMT exerts anti-inflammatory and cytoprotective effects, activating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and the Nrf2-independent pathways[34,41]. Dimethyl fumarate as a potent antioxidant can exert a big role in apoptosis, modulating it. Furthermore, dimethyl fumarate may exert protective effects on the heart, especially against myocardial I/R injury. This drug has been confirmed to suppress cardiovascular disease (such as pulmonary hypertension and diabetic cardiomyopathy) and may be a promising therapy option for patients with acute ischemic heart disease[41].

In addition to the frequently used DMTs, there are pain management drugs that can also be prescribed to improve the quality of life in MS cases, since neuropathic pain is a highly prevalent and debilitating symptom. Ordinary forms of neuropathic pain in MS patients include central neuropathic pain, Lhermitte's phenomenon, and trigeminal neuralgia. The most used opioid analgesics to treat pain are morphine, oxycodone, and tramadol. Opioids are known to lead to bradycardia. Some cannabinoids can be used with the same goal of decreasing pain, the most used of which are dronabinol (THC) and Sativex (THC/CBD). However, the effects of cannabis can increase heart rate and induce vasodilation, causing reflex tachycardia. Anticonvulsants like topiramate, levetiracetam, lamotrigine, carbamazepine, oxcarbazepine, gabapentin, and pregabalin can be used to mitigate pain, though some antiepileptic drugs can induce bradyarrhythmias. Tricyclic antidepressants are considered a well-tolerated second-line treatment for pain management, the most used of which are amitriptyline, nortriptyline, and clomipramine. However, this class of antidepressants can lead to increased heart rate, postural hypotension, and slight prolongation of the intraventricular conduction time and QT interval. Serotonin and noradrenaline reuptake inhibitors like venlafaxine and duloxetine are prescribed with this same goal. These drugs are associated with a small decrease in heart rate and hypotension. Nevertheless, all of these pain management drugs can be prescribed when the potential benefits greatly outweigh the risks[42].

DISCUSSION

As exposed above, MS and cardiac alterations are not uncommon and can be present in any part of MS patient care.

Initially, at the onset, dysautonomia symptoms like POTS can be used as a clinical marker of patients at higher risk of evolving from CIS to MS[21]. Other rare cardiovascular conditions can be a manifestation of MS, such as Takotsubo cardiomyopathy and Brugada syndrome[25].

Adding to this is the interesting relationship between cardiovascular risk factors and MS disease progression, in which higher cardiovascular risk represents an important predictor of disease severity, lesion burden, and disability during the illness[7]. If these results are due to an overlap of cardiovascular and cerebrovascular diseases alone or act through inflammation, driving a more active disease, remains to be clarified.

What is clear is that patients with MS not only progress badly when associated with cardiovascular risk factors but are also at increased risk of cardiovascular morbidity and mortality, including strokes and other major cardiovascular events[3,11]. This could help us explain why patients with MS have higher mortality and shorter life expectancy when compared with the normal population[9,43].

Finally, MS treatments are not innocuous for the cardiovascular system and require attention, especially considering fingolimod and mitoxantrone, which are the two DMTs with the best documentation of cardiovascular complications.

We recommend that MS patients be treated as a whole by the neurologist responsible for patient care, with a careful evaluation of CV risk factors that are possible modifying risk factors for disease progression and disability that should not be ignored. We hope that this review also paves the way for more studies on cardiac abnormalities in

CONCLUSION

In conclusion, MS represents an important and not uncommon cause of burden especially in young adults. Physicians addressing MS patients should be aware of their increased cardiovascular risk and the impact that adequate control of these factors can have on disease progression, patient lifespan, and global care. Cardiovascular disease represents an important cause of mortality in these patients and should be adequately treated in MS patients.

Author Contributions

All authors contributed equally to the design, research and writing of this manuscript.

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