

Comorbidities in Patients with Multiple Sclerosis and How Lifestyle Behaviors Can Change the Comorbidities, Role of the Family Physician and Neurologist

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ABSTRACT

Introduction: Comorbidity can be defined as any additional disease that coexists in an individual with a given index disease, which is not an obvious complication of the index disease. Physical and mental comorbid conditions are common among persons with MS.

Searching Strategy and Selection Criteria: We identified relevant articles in English for this review by searching PubMed, for articles published between January 1, 2017, and Feb 28, 2023, and reference lists from relevant articles.

Comorbidities in MS: The most prevalent comorbidities in MS are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hypercholesterolemia (10.9%), and chronic lung disease (10%).

Lifestyle Behaviors: In the last years, multiple studies shown that the exercise can improve not only the physical part, also the mental health and quality of life. In the recent years several studies concludes that the Paleolithic diet have good results in the relieve of the symptoms of MS like fatigue and the cognitive functions. It's well know that the stress, depression, and anxiety have a high prevalence in MS patients. In one cross-sectional study of RRMS and PMS patients, the patients with RRMS reported a higher emotional support, affection support and positive social interaction.

Conclusion: Having lifestyle changes like exercise, good nutrition and supplementation can reduce the risk of the mention comorbidities also have a positive result in the psychological and social area diminishing symptoms and mental diseases.

Keywords

Multiple sclerosis, Comorbidities, Vascular diseases, Type 1 diabetes, Celiac disease, Thyroid disorders, Cancer, Psychiatric Comorbidities, Lifestyles behaviors, Exercise, Anxiety, Fatigue, Social interactions, Depression, Diet.

Introduction

Comorbidity can be defined as any additional disease that coexists in an individual with a given index disease, which is not an obvious complication of the index disease [1]. Classic definitions of comorbidity do not include health behaviors. However, behaviors such as smoking, alcohol consumption and a sedentary lifestyle affect the risks and the outcomes of chronic diseases, including Multiple sclerosis (MS).

Physical and mental comorbid conditions are common among persons with MS, and these comorbidities are associated with diagnosis delay and increased self-reported disability [2].

Higher prevalence includes affective disorders, cardiovascular disease, systemic autoimmune disorders and epilepsy, chronic lung disease, anxiety, and depression are the most prevalent ones. It is suggested that comorbidities may affect MS disease course, but this interaction is complex, including genetic predisposition, environmental exposure, systemic inflammation, and relationship with disease-modifying therapies (DMT) [3].

Searching Strategy and Selection Criteria

We identified relevant articles in English for this review by

searching PubMed, for articles published between January 1, 2017, and Feb 28, 2023, and reference lists from relevant articles. We used the search terms “multiple sclerosis” (all fields) AND “comorbidity” (all fields) AND [“family physician” (all fields) OR “biopsychosocial” (all fields)]. Preferentially, we chose references published within the past 5 years but also included older key or landmark studies in the field, but some of articles have 10 years of publication and less of 15 years. The final reference list was made based on relevance to the theme of this review.

Comorbidities in MS

The most prevalent comorbidities in MS are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hypercholesterolemia (10.9%), and chronic lung disease (10%) [4].

Vascular Comorbidities

Vascular comorbidity at clinical MS onset or later during MS increases the risk of disability progression. Slower walking speed was found in patients with MS with hypertension or diabetes [4].

Several studies suggest that vascular comorbidities including hypertension, hyperlipidemia, and heart disease may adversely influence disability progression [5].

A higher risk of cardiovascular diseases among persons with MS was confirmed by a registry study from Sweden. Moreover, persons with MS had an overall elevated relative risk for deep vein thrombosis; those with primary progressive MS had a 3-fold higher risk, followed by those with secondary progressive MS and relapsing-remitting multiple sclerosis (RRMS) [6].

A large population-based matched cohort study compared over 12,200 persons with MS registered in the Clinical Practice Research Datalink in England with close to 73,000 controls. Over an 11-years period, patients with MS had 28% increased risk of acute coronary syndrome, 59% increased risk of cerebrovascular disease, and 32% increased risk of any macrovascular disease, which was not completely accounted for by traditional vascular risk factors [7]. According to a recent systematic review and meta-analysis, stroke, and ischemic cerebrovascular event occur more frequently in patients with MS, although there is a gap of knowledge regarding the extent of the risk and the etiological association with MS.

Inflammation in autoimmune diseases can damage the normal physiological function of the endothelium, accelerate the process of atherosclerosis, and increase the risks of cerebrovascular diseases, particularly ischemic stroke. Furthermore, the fatty myelin sheaths around the axons are damaged in the CNS, leading to demyelination, remyelination, axonal loss, gliosis, and neurodegeneration. The condition may persist for months to years and increase the risk of arterial atherosclerosis.

In one systematic review, people with MS displayed an elevated risk of stroke over different periods. A definite conclusion about the most common subtypes of stroke occurring in people with MS was

not reached in a recent study. A study from Finland showed that 6 patients in the MS cohort had experienced a stroke, 5 of whom had experienced an acute ischemic stroke in the large vessels and one of whom had experienced a TIA with a few hours of aphasia. Some potential common risk factors for MS and stroke are listed below. First, obesity in childhood and early adolescence may accelerate the development of MS and increase the intima-media thickness, which is correlated with coronary artery diseases and represents a predictor of stroke.

Second, ischemic stroke may also be induced by T-cells specific to Epstein-Barr virus during the inflammatory reaction in atherosclerotic plaques, as well as low levels of vitamin D, a possible risk factor for MS. Brain-related symptoms observed in people with MS may be caused by vascular epithelial cells, and the demyelination of neurons may lead to a series of ischemic changes in the early phase.

Most individuals with MS also have low levels of physical activity.

Furthermore, MS treatments may also increase the risk of vascular diseases. Systemic glucocorticoids may increase the risk of cerebrovascular and cardiovascular diseases. High-dose glucocorticoid use has been reported to increase the risks of myocardial infarction and stroke. A positive correlation between cardiovascular risk factors and the use of disease-modifying therapies, such as interferon and glatiramer acetate, has been observed [8].

Further studies are needed

Autoimmune Comorbidities

Autoimmune diseases are relatively rare, but their coexistence with MS is reported by several articles, although a small sample size is a common issue in these studies.

In particular, the coexistence of type 1 diabetes mellitus (DM1) is supported by several publications [1]. Sardinia cohort study found a fivefold and twofold higher prevalence of T1D in patients with MS and their first-degree relatives, respectively, compared with the general population. In a Danish cohort study, patients with T1D were at a threefold increased risk for the development of MS, and the risk for T1D in first-degree relatives of patients with MS was increased by approximately 40%. A higher risk was found in an American study carried out in a population of women with T1D, who presented a 20-fold increased risk of developing MS [9].

Several publications have reported the prevalence of gluten-related antibodies among patients with MS. Among six studies estimating the prevalence of seropositivity for anti-gliadin (AGA) immunoglobulins (Ig) in patients with MS, only one study found a significantly higher prevalence of IgG-AGA among patients with MS (7/98) compared to HCs (2/140) ($p = 0.03$). However, when investigating whether patients with MS have elevated mean values of IgA-AGA or IgG-AGA compared to Health controls (HCs), the results are highly contradictory. We can therefore not exclude that patients with MS may have slightly elevated AGA titers compared

to HCs, however, this is still far from sufficiently different for diagnostic use [10].

Thyroid disorders (TD) also seem to affect people with MS more than the general population. However, thyroid dysfunction is a known side effect of some DMTs, particularly alemtuzumab and, to a lesser extent, interferon- β . There are also reports with the use of dimethyl fumarate. Therefore, the part of the autoimmune burden in MS that is independent of DMT-induced thyroid diseases is difficult to establish, but it is important to assess the true causal association.

In one cohort, the incidence of both structural and functional TD was extremely low during and after treatment with DMF (0% and 1.2%, respectively) [11].

Immune reconstitution after drug-induced lymphopenia is an immunologic event which has been observed following graft vs host reaction, active antiretroviral therapy, or alemtuzumab (ALZ) treatment for MS. The thyroid gland represents the preferred target of autoimmune attacks (ATEs) triggered by alemtuzumab during the reconstitution of the lymphocyte repertoire. Moreover, autoimmune thyroids events seem to occur almost exclusively when ALZ is used in patients affected by MS: only anecdotal reports of ATEs after administration of ALZ are depicted in patients with other diseases (i.e., vasculitis and patients receiving cells and organs transplant); yet no ATEs are described when high doses of ALZ are used in patients with Chronic lymphocytic leukemia or rheumatoid arthritis. Therefore, for reasons that remain unclear, MS is a favourable milieu where ALZ may trigger thyroid autoimmunity, so that thyroid dysfunction in alemtuzumab- treated MS patients represent a common challenge in clinical practice [12].

Other autoimmune diseases, such as inflammatory bowel disease and psoriasis [13], were also found to be more prevalent in the population with MS. A recent systematic review found that the risk of inflammatory bowel disease is 50% in the MS population, and the risk of MS has the same magnitude in persons with inflammatory bowel disease with no apparent differences between ulcerative colitis and Crohn's disease [14].

Cancer

In MS population, the results of studies investigating risk for cancer development are conflicting, with some studies reporting higher and others lower risk for malignant diseases compared to the general population. A recent systematic review revealed relative risk for cancer occurrence in MS to be 0.79 (range 0.7–1.67) compared to the background population, indicating lower risk in persons with MS [15].

Data related to the occurrence of breast cancer in persons with MS have been also inconsistent. In one MS cohort, the most common types of malignancy in females were the breast cancer (23.2%) followed by genital cancers, uterine (15.9%) and ovarian cancer (13.0%). Breast cancer risk was slightly reduced in comparison with the general population (SIR = 0.90, 95% CI 0.01–4.99).

Similarly, several studies found no difference in the occurrence of breast cancer in the MS population compared to the general populations [15].

It was recently observed that cancer occurs more frequently among MS patients older than 60 years [16]. It is generally accepted that advancing age is the most important risk factor for cancer overall and for many individual cancer types [17]. Aging is generally accompanied by immunosenescence and chronic low-grade inflammation, which are believed to be associated with the development of a few age-related diseases, including malignancies [18].

Psychiatric Comorbidities

Psychiatric comorbidities are increasingly common in all diseases, especially those that become chronic, and MS is one of them. In a systematic review the more prevalent psychiatric disease was the depression with 30.5% followed by anxiety (21.4%) and sleep disorders [19,20].

Depression is a widely studied pathology in MS being the prevalence peak between 45- 69 years old [21], also in patients with progressive course [22] and patients with fatigue and disability [23]. The early diagnostic of depression in MS will impact their quality of life, cognitive area, sleep quality, fatigue, and physical disability. Several questionnaires have been used to evaluate depression and despite of the variability the prevalence of depression is more in MS patients than general population [21].

The anxiety disorders are less studied than depression but in a systematic review is more related to female gender [21] while in an epidemiological study in Norway the men had more prevalence [23]. In a cross-sectional study of Saudi Arabia females, older people and bad general health state were the factors for more prevalence of anxiety [24].

Like depression anxiety is more common in MS population than general population [24] been the generalized anxiety disorder the most common followed by panic and obsessive compulsive disorder [25]. All anxiety disorders can affect the quality of life, increase the fatigue and decrease cognitive ability and memory [26,27].

There are other pathologies that can occur, however, they have not yet been sufficiently studied, like alcohol and illicit drug use and bipolar disorder with a prevalence of 0 to 16.2 % [28]. It's not a clear prevalence of alcohol intake but the estimated is 3.96% to 18.2% [29]. A case report suggests that the early onset of substance abuse likely to present organic damage [28].

There are many psychiatric symptoms that patients with SM can manifest like somatization, anger-hostility, phobic anxiety, and others [22] but will be need further studies.

Sexual Dysfunction

MS commonly affects young adults with sexual disturbances

having been demonstrated to be present from the onset of the disease and to have a large impact on quality of life at all ages. Sexual dysfunction has been reported to affect up to 50– 90% of men and 40–80% of women.

Most MS patients reporting sexual dysfunction exhibit hypoactive sexual behavior that can be categorized as stemming from deficiencies in sexual interest, arousal, and ejaculatory and orgasmic function. The most common problems reported by men include erectile dysfunction [30].

In a systematic review and metanalysis of Azimi et al. 2019, they reported that in MS women, Sexual Dysfunction (SD) had a widely varying prevalence, ranging between 27% and 95%, and a pooled estimate of 55% (95% CI 41%-69%).

Sexual dysfunction is an issue of concern in MS cases, which is ignored due to cultural issues and religious issues. Physical, psychological, and marital factors could affect SD. Women with MS suffer from a wide range of psychological problems, including depression, anxiety, and stress.

On the other hand, near 75% of MS cases develop voiding dysfunction during the disease course, which influences their sexual function.

Longer disease duration was related with SD in MS, which could be due to the progressive nature of the disease, and medication adverse effects. Zhao et al. found in their meta-analysis that a disease duration longer than 10 years had a 2.5-fold increased risk of SD, although it was not significant.

Expanded Disability Status Scale (EDSS), used to assess physical disability of MS patients, had a significant relationship with SD in previous studies.

Aging is another risk factor of SD. As women get older, they experience dyspareunia and diminished libido, according to hormonal alterations [31].

Lifestyle Behaviors

Exercise

Exercise is a key factor in many diseases. In the last years multiple studies shown that the exercise can improve not only the physical part, also the mental health and quality of life [32,33].

It's been demonstrated that the exercise can be effective for primary prevention to tertiary prevention [34].

In patients with stablished diagnosis, there are several studies in the last 5 years that support the improve of the physical and mental health in MS patients. In 2019, Grazioli et al., published a study with 20 patients, mostly women, to evaluate the improvement of the patients with combined training (resistance and aerobic) resulting of better psychological assessment and diminishing the fatigue and progression of symptoms and disabilities [35].

Also, there are two randomized controlled trials [32,36]; in Langeskov-Christensen et al., with 86 patients with mild to severe impaired MS the group with progressive aerobic exercise improved they cardiorespiratory fitness. Tollár et al., as well proved in their study that the exergaming, balance and cycling improved the MSIS-29 (Multiple Sclerosis Impact Scale-29) and the quality of life. Individually the exergaming improved the gait, balance scores, and with balance improved the risk of falls [32].

A systematic review of 18 studies between 1900 and 2017 concluded that aerobic exercise improves the physical, mental, and social functioning as well as the physiotherapy but no yoga and combination of exercises [33].

Nutrition

In the recent years several studies concludes that the Paleolithic diet have good results in the relieve of the symptoms of MS like fatigue and the cognitive functions [37,38] also the Mc Dougall Diet have these benefits [39]. Other diets like Mediterranean diet, Ketogenic Diet and Hyperbolic diet caloric restrictions decrease the oxidative stress, the inflammation that reflects in markers like IL-6 [39,40]. Mousavi-Shirazi-FardIn et al. in a randomized clinical trial with 100 patients with RRSM (Relapsing Remitting Multiple Sclerosis) in which it was evaluated the quality of life, BMI (Body Mass Index) and serum levels of IL-4, IL-17 and PCR (C-Reactive Protein) the anti-inflammatory diet had positive results in the improvement of quality of life, BMI and IL-4 levels [41].

In 2019, Armon-Omer et al., found that patients with MS in different stages had deficiency of iron, Vitamin D, Vitamin C, Vitamin A and some antioxidants [42]. Even though this study was done, we only have evidence of vitamin D supplementation with safe doses of 10 000 to 40 000 IU/day to avoid high dose complications [43]. More studies are required to continue evaluating the adequate supplementation with vitamin D as well as the other parameters analyzed.

Psychological Factors

It's well know that the stress, depression, and anxiety have a high prevalence in MS patients [44]. Besides the pharmacologic treatment, there are psychological interventions that can be made.

In two systematic reviews of randomized controlled trials, the mindfulness-based therapies and the cognitive behavioral therapy reduced the psychological distress [45], also in another systematic review the psychologic interventions with or without pharmacologic therapy had a mild to moderate positive outcomes for patients with MS [46].

There are two more randomized controlled trials in the recent years that reports a reduction of emotion dysregulation with 4 weeks of mindfulness-based training [47] and another trial with 55 individuals and three arms composed by online chair yoga, mindfulness for multiple sclerosis(M4MS) and mindfulness-based cognitive therapy in a period of 8 weeks resulting the M4MS with acceptability among patients [48]. Giovannetti et al. made a

single-arm longitudinal study in which applied a based group resilience intervention that indeed improved the resilience of these patients but also the anxiety, depression, stress, and health-related quality of life after the intervention [49].

There is no doubt that the psychological part affects the course of MS and it's a topic that we must be aware in future investigations to provide better evidence.

Social Factors

In one cross-sectional study of RRMS and PMS patients, the patients with RRMS reported a higher emotional support, affection support and positive social interaction. In addition, improved the quality of life and anxiety and depression symptoms. However, it must be considered that the sample of the two groups was not equitable, and this can lead to a bias in the results obtained [50].

In Henry et al., they studied the perception of RMMS and PMS patients of social support, depression and anxiety and fatigue. Patients that perceive less social support have more symptoms of depression, anxiety, and fatigue [51].

Social support is a tool that must be used to improve comorbidities of MS patients.

Conclusion

MS is a neurologic disease that is accompanied by organic comorbidities that can further affect the course of this pathology, especially since these comorbidities have cardiovascular, endocrine and autoimmune involvement.

Added to this, the psychological part is also affected, with a high prevalence of depression, anxiety, and other affectations that require further studies. As well, the social part like people interactions and family support can affect the course of MS.

Having lifestyle changes like exercise, good nutrition and supplementation can reduce the risk of the mentioned comorbidities also have a positive result in the psychological and social area diminishing symptoms and mental diseases.

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