

## EFFECTS OF COMORBIDITY IN PERSONS WITH MULTIPLE SCLEROSIS

## UTICAJ KOMORBIDITETA NA TOK MULTIPLE SKLEROZE

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Comorbidity is one of major patients' characteristics, together with genetics, age, gender, race, ethnicity, and socioeconomic status, relevant to the clinical presentation and management of multiple sclerosis (MS). The main goal of investigation of comorbidities in persons with MS is to improve the outcome of the disease and general health of the patients. It is estimated that one in three MS patients is suffering from some physical comorbidity, while more than half of them experience psychiatric comorbidity during course of the disease. Recent systematic reviews revealed that among physical comorbidities, the most prevalent are hypertension, hypercholesterolemia and chronic lung disease, while depression and anxiety are the most frequent among psychiatric comorbidities. Moreover, it was found that the presence of physical comorbidities is associated with the greater risk for the occurrence of mental comorbidities. Although physical and mental comorbidities are increasingly recognized as relevant to clinical outcomes, gaps in the understanding of epidemiological aspects of comorbidity in MS still remain. It is clear that several potential benefits can be gained from the study of comorbidities in patients with MS, including improved prognosis, individualized disease management, insights into the etiology and pathogenesis of MS, and new treatment approaches. Natural history studies conducted so far have focused on the prognostic value of clinical characteristics of this disorder, however, inclusion of comorbidity information could improve prognosis by explaining heterogeneity in disease outcomes, which would enable clinicians to provide individual patients with better information about the clinical course of their disease and to make informed treatment choices. Early identification and treatment of modifiable comorbid conditions represent promising points of MS care which could potentially delay development of sustained worsening disability and improve overall quality of life.

**Keywords:**multiple sclerosis,  
physical comorbidity,  
psychiatric comorbidity,  
prevalence

## Sažetak

Prisustvo komorbiditeta, zajedno sa uzrastom, polom, genetskim predispozicijama, etničkom pripadnošću i socioekonomskim statusom, predstavlja jednu od najznačajnijih karakteristika pacijenata sa multiplom sklerozom (MS), važnu u donošenju odluka o lečenju ove bolesti. Glavni cilj istraživanja komorbiditeta kod osoba sa MS je uticaj na ishod bolesti i sveukupno zdravlje pacijenata. Procenjuje se da jedna od tri osobe sa MS ima neki od somatskih komorbiditeta, dok više od polovine njih tokom trajanja MS dobije i neki od psihijatrijskih komorbiditeta. Rezultati nedavno objavljenih sistematskih pregleda su pokazali da su među somatskim komorbiditetima kod osoba sa MS najčešći hipertenzija, hiperholesterolemija i hronična plućna bolest, dok među psihijatrijskim komorbiditetima najveću učestalost imaju depresija i anksioznost. Osim toga, pokazano je da je prisustvo somatskih komorbiditeta povezano sa povećanim rizikom za nastanak mentalnih komorbiditeta. Iako su somatski i psihijatrijski komorbiditeti prepoznati kao veoma bitni faktori koji utiču na tok MS, još uvek nema dovoljno epidemioloških podataka na tu temu. Proučavanje komorbiditeta može imati mnogo pozitivnih efekata na tok MS, uključujući bolju prognozu bolesti, individualizovani pristup pacijentu, bolje sagledavanje etiologije i patogeneze MS, kao i nove terapijske pristupe. Studije prirodnog toka, sprovedene do sada, fokusirale su se prevashodno na prognostičku vrednost kliničkih karakteristika ovog oboljenja. Uključivanje podataka o komorbiditetima može, međutim, povoljno da utiče na prognozu bolesti objašnjavanjem heterogenosti ishoda bolesti, što bi pomoglo kliničarima u informisanju pacijenata o toku bolesti, kao i u odabiru odgovarajućeg lečenja. Rana identifikacija i lečenje modifikujućih komorbiditeta predstavljaju važan segment na polju istraživanja MS, koji potencijalno može uticati na odlaganje onesposobljenosti i poboljšati sveukupni kvalitet života osoba sa MS.

### Ključne reči:

multipla skleroza,  
somatski komorbiditeti,  
psihijatrijski komorbiditeti,  
prevalencija

## Introduction

The comorbidity is usually defined as the coexistence of two or more medical conditions or diseases in an individual (1). It should be emphasized that comorbidity is related to the burden of entities other than the index disease (2). Additionally, it should be distinguished from complications which are directly linked to the certain illness (3). It is well known that comorbidity is often present in people suffering from chronic diseases. According to literature data, in 2005, number of people living with chronic disease in the USA was greater than 130 million (4). Also, the Center for Disease Control (CDC) reported that in this country, one in four adults have two or more coexisting chronic conditions (5). Bearing in mind that presence of chronic diseases increases with age, on one hand and prolongation of lifespan on the other, it is obvious that number of people living with comorbidity will increase in all parts of the world.

When it comes to neurological disorders, attention for comorbidity has an increasing tendency, and in this light one of the most important entities is multiple sclerosis (MS) (1). Multiple sclerosis is a chronic progressive inflammatory and neurodegenerative disease of the central nervous system (CNS). In 2013, a total of 2.3 million people were living with MS worldwide (6). Comorbidity is one of major patients' characteristics, together with genetics, age, gender, race, ethnicity, and socioeconomic status, relevant to the clinical presentation and management of MS (3).

The main goal of investigation of comorbidities in persons with MS is to improve the outcome of the disease

and general health of the patients (2). Studies conducted so far (7) reported that more than a half of persons with MS have some comorbidity. Additionally, it has been shown that presence of co-occurring diseases can influence a range of outcomes in MS patients (8-11). An increasing amount of evidence suggests that comorbidities might affect the length of time period between MS symptoms onset and diagnosis (9). This time gap is explained in part by masking MS symptoms by comorbidity symptoms (2). Furthermore, comorbidities can affect different decisions regarding choice of adequate therapy, such as decisions about using therapy or not, if decision is to start treatment, which therapy would be the best and most effective, etc. Besides pharmacologic therapy, comorbidity can influence non-pharmacologic treatment as well (2). Additionally, it has been shown that MS patients with one or more comorbidities have a two-fold higher all-cause hospitalization rate than MS patients without any comorbidity (13). A study by Marrie et al. (14) revealed that persons with MS and some vascular comorbidity, have faster progression to an EDSS of 6, approximately 6 years before, compared to persons with MS without vascular comorbidity (14). The presence of comorbidity has negative impact on health-related quality of life and is associated with progression of lesion burden on magnetic resonance imaging as well (2). Finally, within the MS population, comorbidity is associated with a two-fold increased mortality risk (15). The same study showed that although survival of patients with MS has an increasing tendency, their lifespan is still about 7 years shorter, compared to healthy people of the same age, gender and socio-economic status (15). Comorbidities

that had the strongest association with mortality risk were depression, diabetes and ischemic heart disease (15).

## Mechanisms of comorbidity occurrence

A study by Valderas et al. (2009) explained three potential mechanisms of the occurrence of comorbidities, in general (16). First of them refers to presence of two or more distinct conditions in an individual by chance. Second mechanism is related to greater chance of people visiting doctors to get diagnosis of disease and is classified as selection bias. Finally, comorbidity can be consequence of the causal association. This means that: <sup>a)</sup> comorbidity can be caused by the existence of the index disease (direct causation model); <sup>b)</sup> co-occurring diseases share risk factors (associated risk factors model); <sup>c)</sup> two diseases have risk factors which are not associated but can cause both diseases (heterogeneity model); <sup>d)</sup> coexisting diseases can be both related to a third disease (independence model) (17).

## Comorbidity in MS

### *Psychiatric comorbidities*

Generally, comorbidities are divided into physical or mental. It is estimated that one in three MS patients is suffering from some physical comorbidity, while more than half of them experience psychiatric comorbidity during course of the disease (18-21). Recent systematic reviews revealed that among physical comorbidities, the most prevalent are hypertension, hypercholesterolemia and chronic lung disease, while depression and anxiety are the most frequent among psychiatric comorbidities (2). Moreover, it was found that the presence of physical comorbidities is associated with the greater risk for occurrence of mental comorbidities (22,23). This is not a surprising finding, bearing in mind that the presence of chronic diseases is frequently associated with coexistence of mental disorders (24). Also, a study by Marrie et al. (25) revealed that depression and anxiety are more frequent in MS population compared to general population. More recent systematic review confirmed high prevalence of psychiatric comorbidities during MS course, but also at the disease onset (26). According to this study, anxiety is affecting between 1.24% and 36% of MS population (26). When prevalence of depression is calculated based on diagnose not made by questionnaire, it ranges from 3.80% to 68.4% and when it is based on use of questionnaire, estimated prevalence ranges from 6.94% to 70.1% (26). In addition, this study showed that besides depression and anxiety, persons with MS have greater chance to develop bipolar disorder than general population (26).

### *Autoimmune comorbidities*

Research regarding presence of autoimmune diseases in persons with MS is of the particular interest. Keeping in mind the fact that, though etiology of MS is not yet completely understood and it is considered to

be immune-related disease, research about autoimmune comorbidity in these persons can potentially help in clarifying risk factors for MS development (27). The most common autoimmune diseases in MS population, based on the results of the systematic review of 61 studies, are thyroid disease (affecting 2.08-10% of MS population) and psoriasis (present in 0.39-7.74% of MS population). According to literature data, prevalence of majority of autoimmune disorders in MS is less than 5% (27). Exceptions i.e. autoimmune diseases with probably higher prevalence are psoriasis, celiac disease, type 1 diabetes and thyroid disorders (27). The same study reported greater risk for persons with MS to develop inflammatory bowel disease, uveitis and pemphigoid than general population (27).

### *Cancer comorbidity*

The most prevalent cancers in MS population are cervical (reported prevalence ranging from 0.06% to 0.67%), breast (prevalence 0.38-2.3%) and gastrointestinal (prevalence of: esophageal cancer 0.01%, stomach cancer 0.02-0.48%, liver cancer 0.02-0.31%, colorectal cancer 0-0.7%), in accordance with systematic review including 38 different studies evaluating these comorbidities (28). Another finding from this comprehensive study refers to decreased chance of cancer occurrence in persons with MS compared to general population (28). Namely, chance of developing ovarian, testicular, prostate and pancreatic cancer was lower than in general population and on the contrary, brain and urinary cancers were more common in MS population (28). Investigation of these coexisting diseases in MS population is very important due to essential role of immune system in development of both MS and cancer. Some of the explanations for occurrence of malignant diseases in MS are presence of chronic inflammation, as well as the use of immunosuppressive therapy (28).

### *Sleep disorders and seizure disorders*

Keeping in mind the fact that sleep disorders are frequent in non-MS population, it is not surprising that prevalence of these disorders is also high in MS. Sleep disorders affect many aspects of individual's life, and can have significant influence on people with MS due to its chronic nature. Among sleep disorders in MS, researches usually focus on restless legs syndrome and sleep apnea. Prevalence of restless legs syndrome vary from 14.4% to 57.5% (29). The prevalence of sleep apnea is quite similar, between 7.14% and 58.1% (29). On the other hand, data from population-based studies revealed that incidence of seizures in MS population is about 2.28% and the prevalence is 3.09% (29). Risk for development of seizures in persons with MS is greater than in general population, which is partially explained by presence of inflammation and demyelization in these persons (29).

### *Cardiovascular comorbidity*

There is emerging evidence that vascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus

and ischemic heart disease can negatively affect many aspects of MS, including level of disability, health-related quality of life, MRI lesions (30,31). The leading cardiovascular comorbidities in MS population are hypertension (prevalence ranging from 0% to 47.8%), hyperlipidemia (prevalence ranging from 3% to 47.8%) and diabetes (prevalence ranging from 0% to 27.1%) (32). Also, presence of these comorbidities correlates with older age and male gender (32). The prevalence of ischemic heart disease and stroke was reported to be lower than 5% (32). Generally, persons with MS have greater chance for development of ischemic heart disease, congestive heart failure, ischemic stroke and peripheral vascular disease (32). This association might be a consequence of high prevalence of risk factors for cardiovascular diseases in MS population, particularly smoking, weight excess and low physical activity.

### Other comorbidities

Besides aforementioned diseases, gastrointestinal, musculoskeletal and pulmonary illnesses are frequent in MS population (33). Comorbidities with the highest prevalence are irritable bowel syndrome and chronic lung disease (estimated prevalence is over 10%) (26). Among musculoskeletal disorders, arthritis is frequent (reported prevalence is between 2.97% and 26%), while among ocular diseases, leading comorbidities are glaucoma (prevalence ranging from 0.74% to 12.1%) and cataracts (prevalence ranging from 1.24% to 3.5%) (33). The prevalence of renal disease is about 2.5% (33). However, all these values should be interpreted with caution, bearing in mind small number of studies investigating this topic.

### Key problems in research of comorbidity in MS

Although physical and mental comorbidities are increasingly recognized as relevant to clinical outcomes, gaps in the understanding of epidemiological aspects of comorbidity in MS still remain (29). Firstly, studies of the frequency of comorbidity in MS, compared with the general population, are rarely designed as population-based (8). Moreover, data on the prevalence of comorbid conditions in MS is characterized by significant variations, influenced by many factors including number and type of investigated diseases and study population features. Not surprisingly, assessments of incidence of specific comorbidities are even of less validity. Although it is well known that population characteristics differ worldwide, age- and gender-specific incidence or prevalence of comorbidities in MS population are infrequently stated (8). Additionally, rates are rarely standardized according to standard population in order to allow for international comparisons. Precise estimates of risk for development of some comorbidity (incidence) and its distribution (prevalence) are needed for examination of temporal trends in comorbidity occurrence, which may help in determination of changes in population characteristics or specific exposures (8). Also, exact values of incidence and prevalence of different comorbidities can help in post-marketing pharmacovigilance (8).

### Conclusion

Keeping in mind all previously mentioned, it is clear that several potential benefits can be gained from the study of comorbidities in patients with MS, including improved prognosis, individualized disease management, insights into the etiology and pathogenesis of MS, and new treatment approaches. Natural history studies conducted so far have focused on the prognostic value of clinical characteristics of this disorder, however, the inclusion of comorbidity information could improve prognosis by explaining heterogeneity in disease outcomes, which would enable clinicians to provide individual patients with better information about the clinical course of their disease and to make informed treatment choices. Early identification and treatment of modifiable comorbid conditions represent promising points of MS care which could potentially delay development of sustained worsening disability and improve overall quality of life.

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