







## RESEARCH ARTICLE

# Autoimmune comorbidities in persons with multiple sclerosis in the population of Belgrade

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Received: 12 August 2022

Revised: 13 September 2022

Accepted: 18 September 2022



Check for updates

## Funding information:

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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## Competing interests:

The authors have declared that no competing interests exist

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## Summary

**Aim of the paper:** To analyze the burden of autoimmune comorbidities in persons with multiple sclerosis (PwMS) in Belgrade, Serbia, using the population-based MS Registry.

**Methods:** A descriptive epidemiological study was used. The source of data was the Belgrade population MS Registry. The prevalence of different autoimmune comorbidities was calculated as the proportion of persons with a certain comorbidity among the total MS cohort in the Registry and presented with corresponding 95% Confidence Interval (CI). The prevalence date used was December 31st, 2021.

**Results:** The prevalence of all autoimmune comorbidities was 5.80% (95% CI 4.98-6.73) i.e. the total of 165 autoimmune comorbidities were registered in 2841 PwMS in the Belgrade Registry on December 31, 2021. The highest prevalence was observed in autoimmune thyroid disease (4.26%, 95% CI 3.55-5.07). The highest prevalence was observed in the age groups 50-59 and 60-69 years, with higher values observed in women of all ages. Age-adjusted prevalence of autoimmune comorbidities was 0.05/100,000 in both sexes, 0.03/100,000 in males and 0.07/100,000 in females. In persons with relapsing MS phenotype prevalence of autoimmune comorbidities was 5.5%, while in persons with primary progressive MS phenotype it was 4.9%, however, this difference was not statistically significant ( $\chi^2=5.118$ ;  $p=0.163$ ).

**Conclusion:** The results of our study showed that the prevalence of autoimmune comorbidities in PwMS in Belgrade, Serbia, is in accordance with that observed in other studies. As expected, the prevalence increased with age and was higher in females. The most common autoimmune comorbidity was the autoimmune thyroid disease.

**Keywords:** prevalence, registry, autoimmune thyroid disease

Cite this article as: Maric G, Tamas O, Jovanovic A, Veselinovic N, Ivanovic J, Jovicevic V, Andabaka M, Ilic M, Mesaros S, Pekmezovic T, Drulovic J. Autoimmune comorbidities in persons with multiple sclerosis in the population of Belgrade

Medicinska istraživanja 2022; 55(2):31-36 DOI: 10.5937/medi55-39621

## INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that can lead to severe disability and death (1, 2). It is characterized by huge clinical heterogeneity, however the majority of patients experience slow and continuous progression of vision, motor and sensory impairment (2). Disease predominantly occurs in young females at the mean age ranging from 10 to 60 years (2). The MS atlas in 2020 reported that there were 2.8 million people living with MS at the global level (prevalence - 36 cases per 100,000 inhabitants) and that there were 11,972 in Serbia with a corresponding prevalence of 136 MS cases per 100,000 inhabitants (3). This is a significant increase compared to the data from the previous edition of MS Atlas in 2013, when the total of 2.3 million PwMS were registered (3).

Term comorbidity usually refers to those diseases that occur in an individual apart from the index disease and are frequently present in persons with MS (PwMS) (4, 5). In 2015, Ruth Ann Marrie published seven systematic reviews related to comorbidity burden in MS population (6-12). The investigation of comorbidities in this population has been shown to be of particular significance since there is evidence that the presence of these disorders can negatively affect MS course in several ways. First, comorbidities are associated with an increased disability level and a higher mortality rate among PwMS (13-16). Second, the presence of comorbidity can lead to a prolonged time interval in establishing the MS diagnosis (17). Third, these diseases can result in decreased quality of life in PwMS (18, 19). Despite all this, precise measurements of the comorbidity burden in MS are lacking and there are several reasons for it, including different sources of data, various study designs, lack of age-specific and age-adjusted rates of comorbidity frequency and distribution, etc. (6).

According to previous studies it was demonstrated that PwMS most frequently experience hypertension, hyperlipidemia, chronic lung disease, anxiety and depression as comorbid conditions (20). Among different diseases, autoimmune comorbidities are specially important having in mind that MS is considered to be an autoimmune disease in whose pathogenesis cellular immunity (CD4+ and CD8+ cells) plays an important role, through cells directed at myelin antigens in the CNS (21). Furthermore, autoantibodies may also take part in the development of the disease (21). Therefore, it is assumed that MS and other autoimmune disorders can share at least some risk factors. Consequently, elucidating their etiology could be beneficial for revealing MS etiology, yet incompletely discovered.

According to the results of the studies that investigated distribution of autoimmune diseases in MS patients after establishing MS diagnosis, their frequency in this population ranges from 3% to 26.1% (7). Also, studies have shown that the prevalence of autoimmune diseases is higher in the population of PwMS compared to the general population

(7). Based on the systematic review from 2015 which included 61 different studies, the most prevalent autoimmune comorbidities in these patients were psoriasis (observed in 0.39%-7.74% of MS patients) and thyroid gland disease (observed in 2.08%-10% MS patients) (7). The prevalence of autoimmune comorbidities in MS population is usually below 5%, with several exceptions including previously mentioned thyroid disease and psoriasis, as well as type 1 diabetes and celiac disease (7). The risk of type 1 diabetes was especially examined in Sardinia whose population is well known for its genetic susceptibility to autoimmune diseases occurrence (22-24). Comparison of the risk between MS and general population on this island resulted in finding that the MS population was five times more likely to develop type 1 diabetes than the general population (22).

Autoimmune comorbidities were also studied in Danish population, which has a long tradition of collecting data on MS patients. According to the obtained data, compared to the general population, patients with MS had an increased risk of developing ulcerative colitis and pemphigoid (25). Also, according to research results, first-degree relatives of MS patients had an increased risk of developing some other autoimmune diseases (25).

Taking into consideration all previously mentioned, the aim of this study was to analyze the burden of autoimmune comorbidities in PwMS in Belgrade, Serbia, using the population-based MS Registry.

## MATERIAL AND METHODS

In order to determine the prevalence of autoimmune comorbidities in persons with MS in Belgrade, Serbia, a descriptive epidemiological study was used. The source of data was the Belgrade population MS Registry which contains all the relevant data on each person with confirmed MS diagnosis living in the region of Belgrade. The list of examined autoimmune comorbidities included autoimmune thyroid disease, inflammatory bowel disease, Sjogren's syndrome, vitiligo, psoriasis, rheumatoid arthritis, uveitis, systemic lupus erythematosus, dermatomyositis, systemic sclerosis, pernicious anemia and primary biliary cirrhosis.

The prevalence of different autoimmune comorbidities was calculated as the proportion of persons with a certain comorbidity among the total MS cohort in the Registry. The prevalence date used was December 31<sup>st</sup>, 2021. The prevalence was presented with corresponding 95% Confidence Interval (CI) for each comorbidity separately as well as for all autoimmune comorbidities combined. In order to allow the comparison of prevalence with similar international studies, the direct age-adjustment method was used with both European and World standard populations. Additionally, the prevalence was calculated in relation to different MS phenotypes (relapsing vs. primary progressive). All analyses were performed using Statistical Package for Social Sciences (SPSS), version 17.0.

## RESULTS

The prevalence of autoimmune comorbidities in Belgrade MS cohort is presented in **Table 1**. The prevalence of all autoimmune comorbidities was 5.80% (95% CI 4.98-6.73) i.e. the total of 165 autoimmune comorbidities were registered in 2841 persons with MS in the Belgrade Registry on December 31, 2021. When autoimmune comorbidities were analyzed separately, the highest prevalence was observed for autoimmune thyroid disease (4.26%, 95% CI 3.55-5.07) (**Table 1**). On the other hand, dermatomyositis, pernicious anemia and primary biliary cirrhosis were the least common diseases (for all three comorbidities the prevalence was 0.04%; 95% CI 0.00-0.20) (**Table 1**).

**Table 2** contains age-and-gender-specific as well as age-adjusted prevalence of autoimmune disorders. The highest prevalence of autoimmune comorbidities in PwMS in Belgrade region was observed in age groups 50-59 and 60-69 years, with higher values observed in women of all ages.

Age-adjusted prevalence of autoimmune comorbidities was 0.05/100,000 in both sexes, 0.03/100,000 in males and 0.07/100,000 in females. The values were the same in both cases when European or World standard population was used (**Table 2**).

When the prevalence was analyzed in relation to different MS phenotypes it was shown that in persons with

relapsing MS phenotype the prevalence of autoimmune comorbidities was 5.5%, while in persons with primary progressive MS phenotype it was 4.9%, however, this difference wasn't statistically significant ( $\chi^2=5.118$ ;  $p=0.163$ ).

## DISCUSSION

Autoimmune comorbidities were present in 5.80% (95% CI 4.98-6.73) of MS patients in our cohort. The most frequent autoimmune disease was thyroid disease (prevalence 4.44%, 95% CI 3.71-5.30). This is in accordance with Marrie et al. and their systematic review combining 61 primary studies in which it was reported that the prevalence of autoimmune diseases in MS patients ranged from 3.0% to 26.1%, (7). A study from Sweden revealed that PwMS were at a greater risk of developing an autoimmune disease compared to the general population (IRR=3.83, 95% CI 3.01-4.87) (27). Hauer et al. demonstrated similar findings of more frequent autoimmune comorbidities among PwMS compared to those without MS, particularly in case of psoriasis, rheumatoid arthritis, and inflammatory bowel disease (28).

The most common autoimmune disorder in our MS cohort was autoimmune thyroid disease (4.44%, 95% CI 3.71-5.30). Systematic review with meta-analysis on this group of comorbid conditions in PwMS observed a higher prevalence of thyroid disease (6.44% (95% CI 0.19-12.7))

**Table 1.** Prevalence of autoimmune comorbidities in Belgrade MS cohort

Comorbidity	Prevalence (%)	95% Confidence Interval
Autoimmune thyroid disease	4.26	3.55-5.07
Sjogren's syndrome	0.35	0.17-0.65
Inflammatory bowel disease	0.32	0.15-0.60
Vitiligo	0,21	0.08-0.46
Psoriasis	0.14	0.04-0.36
Rheumatoid arthritis	0.14	0.04-0.36
Uveitis	0,14	0.04-0.36
Systemic lupus erythematosus	0.07	0.01-0.25
Systemic sclerosis	0.07	0.01-0.25
Dermatomyositis	0.04	0.00-0.20
Pernicious anemia	0.04	0.00-0.20
Primary biliary cirrhosis	0.04	0.00-0.20
Total	5.80	4.98-6.73

**Table 2.** Age-and-sex-specific and age-adjusted prevalence of autoimmune comorbidities in Belgrade MS cohort

Age	20-29	30-39	40-49	50-59	60-69	70+	Age-adjusted prevalence*	Age-adjusted prevalence**
Sex								
Male	3.38	2.73	4.99	3.17	1.29	1.69	0.03	0.03
Female	5.76	5.30	7.12	9.08	9.01	3.48	0.07	0.07
Total	4.89	4.54	6.43	7.25	7.00	2.91	0.06	0.06

\*according to World standard population

\*\*according to European standard population

in comparison to our sample (7). Many studies have been performed in order to compare the prevalence of autoimmune thyroid disease in PwMS and general population. The results of these studies are conflicting – some studies found an increased prevalence among PwMS while the others found no difference (29-32). However, systematic review combining the results of 61 individual studies regarding autoimmune comorbidities in PwMS reported that the prevalence of autoimmune thyroid disease was in accordance with the prevalence observed in the general population (7). According to a UK study, a greater risk of autoimmune thyroid disease occurrence is expected in the relatives of PwMS (7). The occurrence of autoimmune thyroid disease in PwMS was also examined in relation to immunomodulatory therapy. It was observed that MS patients undergoing the treatment with interferon- $\beta$  were at a greater risk of developing autoimmune thyroid disease or worsening the existing comorbidity, while a negative impact wasn't observed in patients treated with glatiramer acetate (34-37). Furthermore, it has been shown that autoimmune diseases are the most frequent negative effect of Alemtuzumab treatment and among them Graves' disease is the most common disorder occurring in 16.7-41.0% of MS patients using this therapy (38).

The prevalence of Sjogren's syndrome - 0.35% (95% CI 0.17-0.65) and inflammatory bowel disease - 0.32% (95% CI 0.15-0.60) in our study were also in accordance with previously published findings (0% - 16.7% for Sjogren's syndrome and 0.36% - 4.66% for inflammatory bowel disease) (7). Autoimmune comorbidities with the lowest prevalence in PwMS in the population of Belgrade were dermatomyositis, pernicious anemia and primary biliary cirrhosis (for all three comorbidities the prevalence was 0.04%, 95% CI 0.00-0.20). According to literature, the prevalence of primary biliary cirrhosis in PwMS ranges from 0% to 0.12%, the prevalence of dermatomyositis is estimated to be 0.03% and the prevalence of pernicious anemia ranges from 0% to 2.44% (7).

The results of this study showed that the highest prevalence of autoimmune comorbidities in PwMS in Belgrade was observed at the age of 50-59 and 60-69 years. This is in accordance with the data from earlier research demonstrating that the prevalence of comorbidities increases with MS patients' age (39). Also, in all age groups, the prevalence was higher in female population. This is not surprising having in mind that the majority of autoimmune diseases occur more frequently in women.

The presence of autoimmune comorbidities can potentially negatively influence MS course in several ways. A number of studies showed that the presence of autoimmune comorbidities in PwMS, especially psoriasis and thyroid disease, was associated with considerably worse MRI findings showing significant areas of demyelination (39). In a study based on self-reported data from MS patients, a greater number of comorbidities occurring simultaneously in the same person was associated with

poorer quality of life and an increased level of disability (39). Furthermore, the presence of rheumatoid arthritis was associated with a three-fold higher risk, and the presence of anemia with a twofold higher risk of relapse in MS patients (39). A study performed in New York confirmed a negative influence of autoimmune comorbidities on the brain volume in PwMS, and a relationship was observed for type 2 diabetes, psoriasis and thyroid disease (40). Impaired glucose metabolism in PwMS has been previously documented (41). It has been also shown that type 1 diabetes comorbidity in PwMS is related to an increased brain atrophy as a marker of brain damage, specifically in grey matter and cortical grey matter (42). The level of observed brain atrophy was directly correlated with type 1 diabetes duration (42). However, this correlation has not been found in the case of autoimmune thyroiditis and celiac disease (42).

The strengths of our study include population-based study design. Namely, the Belgrade MS Registry was initiated in 1996 and it is being regularly updated. In Denmark, MS Registry was established in 1948 (43). On the other hand, none of the countries in the Southeast Asian region has MS registries, while 20% of African countries and 22% of countries in the Western Pacific region maintain MS registries. The WHO regions with the largest share of countries with MS registries are the Americas (47%) and the region of Europe (46%) (3). The limitations of our study include a cross-sectional study design taking into account only the presence of autoimmune disorder and no other relevant characteristics of these comorbidities. The other limitation refers to the unavailability of data on comorbidity presence in some patients from the Registry. Finally, not all autoimmune comorbidities were included in the analysis.

## CONCLUSIONS

The results of our study showed that the prevalence of autoimmune comorbidities in PwMS in Belgrade, Serbia, was in accordance with that observed in other studies. As expected, the prevalence increased with age and was higher in females. The most common autoimmune comorbidity was autoimmune thyroid disease. Since it has been shown that the presence of these comorbidities is associated with many negative outcomes in PwMS it calls for action and development of strategies for early detection and treatment of autoimmune comorbidities in order to preserve brain volume, prevent brain damage and avoid negative impact on different MS outcomes.

## Acknowledgments

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Grant/Award Number:200110.

## Conflict of interest

None to declare.

## Author contributions

Conceptualization, J.D., T.P. and S.M.; methodology, G.M., and T.P.; statistical analysis, G.M. and A.J.; measurement and data acquisition, O.T., N.V., J.I., V.M., M.A., and M. I.; writing—original draft preparation, G.

M.; all authors have read and agreed to the final version of the manuscript.

## Ethical approval

Study approval statement: This study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, Serbia, approval number [29/III-17].

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## KOMORBIDITETI AUTOIMUNIH BOLESTI KOD OSOBA SA MULTIPLIOM SKLEROZOM U POPULACIJI BEOGRADA

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### Sažetak

**Cilj rada:** Analiza opterećenja autoimunim komorbiditetima osoba sa multiplom sklerozom (MS) u populaciji Beograda na osnovu podataka populacionog MS registra.

**Materijal i metode:** Sprovedena je deskriptivna epidemiološka studija. Izvor podataka bio je populacioni registar za MS Beograda. Prevalencija različitih autoimunih komorbiditeta je računata kao proporcija osoba sa tim komorbiditetom među svim osobama u registru i prikazana sa odgovarajućim 95% intervalom poverenja (IP). Prevalencija je određivana za dan 31. decembar 2021. godine.

**Rezultati:** Ukupna prevalencija svih autoimunih komorbiditeta iznosila je 5,80% (95% IP 4,98-6,73), odnosno ukupno je registrovano 165 komorbiditeta kod 2841 osobe sa MS u registru za područje Beograda na dan 31. 12. 2021. godine. Najviša prevalencija je zabeležena za autoimunu bolest štitaste žlezde (4,26%, 95%

IP 3,55-5,07). Najviša uzrasno-specifična prevalencija registrovana je u uzrastu 50-59 i 60-69 godina, sa višim vrednostima u ženskoj populaciji u svim uzrastima. Standardizovana prevalencija autoimunih komorbiditeta iznosila je 0,05/100.000 za oba pola, 0,03/100.000 u populaciji muškaraca i 0,07/100.000 u populaciji žena. Prevalencija autoimunih komorbiditeta kod osoba sa relapsnom formom MS bila je 5,5%, a kod primarno-progresivne forme 4,9%, bez statističke značajnosti ( $\chi^2=5,118$ ;  $p=0,163$ )

**Zaključak:** Rezultati naše studije pokazali su da je prevalencija autoimunih komorbiditeta kod osoba sa MS u populaciji Beograda u skladu sa onom dobijenom u drugim studijama. Očekivano, prevalencija je rasla sa uzrastom i bila je viša u populaciji žena. Najčešći autoimuni komorbiditet je autoimuna bolest štitaste žlezde.

**Ključne reči:** prevalencija, registar, autoimuna bolest štitaste žlezde

**Primljen:** 12.08.2022. | **Revizija:** 13.09.2022. | **Objavljen:** 18.09. 2022

**Medicinska istraživanja 2022; 55(2):31-36**