

COMORBIDITIES IN PATIENTS WITH MULTIPLE SCLEROSIS IN CROATIA

Marija Bošnjak Pašić^{1,2}, Katarina Ivana Tudor³, Filip Mustać⁴, Fabijan Rajič⁵, Hanna Pašić⁶,
Luka Vujević⁶, Helena Šarac^{7,8} & Branka Vidrih^{9,10}

¹Referral Center for Demyelinating Diseases of the Central Nervous System, Unit for Neuroimmunology of Central Nervous System, Clinical Department of Neurology, University Hospital Center Zagreb, Zagreb, Croatia

²School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

³Department of Neurology, Unit for Headaches, Neurogenic Pain and Spinal Disorders, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

⁴Department of Psychiatry, University Hospital Centre Zagreb, Zagreb, Croatia

⁵Croatian Football Federation, Zagreb Football Association, Zagreb, Croatia

⁶University of Zagreb, School of Medicine (Medical Studies in English), Zagreb, Croatia (student)

⁷Department of Neurology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

⁸Croatian Institute for Brain Research, Centre of Excellence for Basic, Clinical and Translational Neuroscience, University of Zagreb, School of Medicine, Zagreb, Croatia

⁹Department of Psychiatry, University Hospital Centre Sisters of Mercy, Croatia

¹⁰Catholic University of Croatia, Zagreb, Croatia

SUMMARY

Background: Comorbidities in multiple sclerosis (MS) have a big role in management of this chronic demyelinating neurodegenerative disorder. The aim of this study was to evaluate comorbidities in patients with MS in Croatia.

Subjects and methods: This was a prospective cross-sectional study carried out in an out-patient setting at a tertiary healthcare centre over 10 months, which included 101 consecutive patients with MS (mean age 42.09 (range 19-77) years, 75 female, 26 male, EDSS score 3.1 (range 0.0-7.0)). The average duration of the disease was 13.5±7.487 (range 1-42) years. Thirty-six patients were treated with disease modifying therapies (DMTs). Information on comorbidities was obtained during the medical interview. Data was analysed using software package IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results: 33% (n=34) patients did not have any comorbidities, and there is an equal number of patients (n=34, 33%) that just had one comorbidity. 17.6% (n=18) of patients had two comorbidities, and 15.7% (n=16) three or more comorbidities. The most frequent comorbidity was depression found in 25 (24.75%) patients (19 (18.8%) women, 6 (5.9%) men), followed by the hypertension in 12.87% (n=13). Hyperlipidemia and migraine were each found in 6.93% (n=7), and hypothyreosis and arrhythmia each in 3.96% (n=4). The number of the comorbidities was found to significantly increase with the duration of MS ($r=0.232$, $p=0.037$). Women were found to have significantly bigger numbers of comorbidities than men ($t=-2.59$, $df=74$, $p<0.05$). Older patients with MS were found to have significantly more comorbidities ($r=0.335$, $p<0.01$).

Conclusions: This study gives insight into the presence of comorbidities in Croatian patients with MS. Connection with comorbidities must be considered when managing patients with MS. Any other comorbidity in MS may also affect the condition of the patient in general, and also their quality of life, and requires a tailored approach in management.

Key words: multiple sclerosis (MS) – comorbidities – Croatia – depression - vascular risk factors (VRFs) - migraine

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INTRODUCTION

Previous study assessing epidemiology of multiple sclerosis (MS) from 1990 to 2016 reported 2 221 188 prevalent cases of MS (95% uncertainty interval (UI) 2 033 866–2 436 858) globally, and in Croatia 2019 (1792 to 2262), which corresponded to a 10.4% (9.1 to 11.8) increase in the age-standardised prevalence since 1990 globally, and in Croatia 25.3% (19.6 to 30.7) (Collaborators 2019). Comorbidities in MS have a big role in management of this chronic demyelinating neurodegenerative disorder. Previous studies have shown that certain comorbidities and lifestyle factors have an

influence on disease activity, disability, mortality and overall quality of life (QoL).

Earlier evidence suggested that physical and mental comorbidities, and adverse health factors such as smoking and obesity may affect the disease (Marrie & Horwitz 2010).

Some propose vitamin D supplementation, tobacco smoking cessation, routine exercise, a plant-based, anti-inflammatory diet, and maintenance of emotional well-being as adjunct to disease modifying therapies (DMTs) (Moss et al. 2017).

The aim of this paper was to assess and evaluate comorbidities in our group of patients with MS.

SUBJECTS AND METHODS

This was a prospective cross-sectional study carried out in an out-patient setting at a tertiary healthcare centre (University Hospital Centre Zagreb, Croatia) over 10 months. Research was approved by the local Ethics Committee. Hundred and one consecutive patient with MS (75 female, 26 male, mean age 42.09 (range 19-77) years, mean Expanded Disability Status Scale (EDSS) score 3.1 (range 0.0-7.0). The average duration of the disease was 13.5±7.487 (range 1-42) years. Ninety-five patients with relapse-remitting MS (RRMS), 5 with secondary progressive MS (SPMS), and one patient with primary progressive MS (PPMS) participated in this study (Table 1). Thirty-six patients were treated with DMTs (Table 2).

Information regarding comorbidities was obtained during the medical interview.

Data was analysed using software package IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp., using descriptive statistics, t-test, Pearson correlation coefficient, chi-square test, and a p-value<0.05 was considered to be significant.

RESULTS

33% (n=34) patients did not have any comorbidities, and there is an equal number of patients (n=34, 33%) that just had one comorbidity. 17.6% (n=18) of patients had two comorbidities, and 15.7% (n=16) three or more comorbidities.

Table 1. Patients with MS that participated in this study

Patients with MS	N=101
Gender	
Female	75 (84.26%)
Male	26 (29.21%)
Age	42.09 (range 19-77)
EDSS (0-10)	3.1 (range 0.0-7.0)
Type of MS	
RRMS	95 (94.05%)
SPMS	5 (4.95%)
PPMS	1 (0.99%)
PRMS	0

MS - multiple sclerosis; EDSS - Expanded Disability Status Scale; RRMS - relapse-remitting multiple sclerosis; SPMS - secondary progressive multiple sclerosis; PPMS - primary progressive multiple sclerosis; PRMS - progressive-relapsing multiple sclerosis

Table 2. Disease modifying therapies taken by patients with MS included in this study

DMTs	N=36 (35.64%)
Injectable medications	
Glatiramer acetate	Copaxone n=9 (8.91%)
Interferon beta	Avonex n=5 (4.95%)
	Rebif n=11 (10.89%)
	Betaferon n=7 (6.93%)
	Extavia n=1 (0.99%)
Oral medications	
Teriflunomide	Aubagio n=2 (1.98%)
Dimethyl fumarate	Tecfidera n=1 (0.99%)

DMTs - disease-modifying therapies

Table 3. Comorbidities listed in the order of appearance

	n	%	Women	Men
Depression	25	24.75%	19 (18.8%)	6 (5.9%)
Hypertension	13	12.87%	12 (11.88%)	1 (0.99%)
Hyperlipidemia	7	6.93%	7 (6.93%)	0
Migraine	7	6.93%	7 (6.93%)	0
Hypothyreosis	4	3.96%	4 (3.96%)	0
Arrhythmia	4	3.96%	4 (3.96%)	0
History of appendectomy	4	3.96%	3 (2.97%)	1 (0.99%)
History of cholecystectomy	4	3.96%	3 (2.97%)	1 (0.99%)
Anaemia	3	2.97%	3 (2.97%)	0
Arthritis	3	2.97%	3 (2.97%)	0
History of eye surgery	3	2.97%	2 (1.98%)	1 (0.99%)
Nicotinism	3	2.97%	2 (1.98%)	1 (0.99%)
Osteopenia	3	2.97%	2 (1.98%)	1 (0.99%)
History of head trauma	3	2.97%	2 (1.98%)	1 (0.99%)
Diabetes mellitus	2	1.98%	2 (1.98%)	0
Epilepsy	2	1.98%	2 (1.98%)	0
Mb Crohn	2	1.98%	2 (1.98%)	0
History of cerebellar infarct	2	1.98%	2 (1.98%)	0
Other (n=1)	39	38.61%	30 (29.70%)	9 (8.91%)

The most frequent comorbidity was depression found in 25 (24.75%) patients (19 (18.8%) women, 6 (5.9%) men), followed by the hypertension in 12.87% (n=13) of patients. Hyperlipidemia and migraine were each found in 6.93% (n=7), and hypothyreosis and arrhythmia each in 3.96% (n=4) (Table 3). Average age of patients with vascular risk factors hypertension, hyperlipidemia and diabetes mellitus was 54.05±11.63 (35-77) years, and the average age of patients with arrhythmia 46.75±9.03 (39-59) years. Eighty patients (79.20%) were on add-on therapy with vitamin D.

The number of the comorbidities was found to significantly increase with the duration of MS ($r=0.232$, $p=0.037$).

Women were found to have significantly bigger number of comorbidities than men ($t=-2.59$, $df=74$, $p<0.05$) in t-test, while chi-square test did not show any difference in number of one or more comorbidities between men and women ($\chi^2=1.298$, $df=1$, $p>0.05$). However Pearson correlation coefficient showed significant correlation ($r=0.197$, $p<0.05$) with women having significantly more comorbidities. There were no significant differences between female and male patients regarding treatment for depression ($\chi^2=0.018$, $df=1$, $p>0.05$).

Correlation according to the type of MS was not possible since almost all patients had RRMS.

Older patients with MS were found to have significantly more comorbidities ($r=0.335$, $p<0.01$).

We did not find any correlation between EDSS and the number of comorbidities ($r=-0.71$, $p>0.05$).

DISCUSSION

Some comorbidities were found not only to occur with increased prevalence in patients with MS but to also increase the risks of developing the disease, delayed diagnosis, relapse, and disability progression (Tobin 2019). This study was undertaken to assess and evaluate comorbidities in our group of patients with MS. Among commonly reported comorbidities that were found to have an impact on the diagnosis and disease course are depression, anxiety, hypertension, migraine, hyperlipidaemia and others (Tobin 2019). Albeit we are overall talking about smaller numbers, comorbidities found by our study were found to overlap with previously reported comorbidities found in patients with MS. In the previous two papers we evaluated lower urinary symptoms and sexual dysfunction symptoms in our group of MS patients and they were not the focus of this paper (Pasic et al. 2019). Study investigating epidemiology of comorbidities among MS patients in northeastern Poland using different means (the patients' medical records (with ICD 10 coding) and National Health Fund (NHF) data) found that the most common comorbidity in the MS population was hypertension.

The MS population had an increased prevalence of depression versus the matched controls. MS patients- especially men and older individuals- were found to be at increased risk of developing vascular diseases (Kapica-Topczewska et al. 2020). In our group of patients the most present comorbidity was depression found in 24.75% of patients, followed by hypertension (12.87%) and hyperlipidaemia (6.93%). Our group of patients with MS mostly consisted of women, and similarly comorbidities were significantly more often found in women. The results of our study show that older patients with MS have significantly more comorbidities. Average age of patients (both mean and median) with vascular risk factors hypertension, hyperlipidaemia and diabetes mellitus was around 55 years, ranging from as young as 35 years to up to 77 years of age, while the average age of patients with arrhythmia was 46.75±9.03 (39-59) years. This is important since cardiovascular pathology was found to significantly contribute to worse clinical and magnetic resonance imaging (MRI)-derived disease outcomes in MS. Also it was found that global and regional cerebral hypoperfusion may be associated with poorer physical and cognitive performance (Jakimovski et al. 2019). Patients with MS and healthy controls may exhibit different alpha-adrenergic responses to Valsalva maneuver, which could explain the connection between MS and increased cardiovascular risk (Habek et al. 2018). Previous evidence points to a potential relationship between physical activity and exercise and risk factors related to vascular comorbidities in people with MS, which could represent an effective therapeutic strategy for managing vascular comorbidities in people with MS (Ewanchuk et al. 2018).

At present, as reported by Goischke, MS therapy is still a balancing act between therapeutically efficient action and the management of unexpected side effects, with vitamin D add-on therapy being almost unproblematic and most likely to be accepted by patients with MS (Goischke 2019). Similarly, in our group of patients with MS, around 80% of patients were on add-on therapy with vitamin D. A little over one-third of patients were found to be treated with DMTs. The majority of patients with MS were treated with interferon beta, possibly due to the affordability and due to their longer availability in the market (Zaprutko et al. 2017, Zadro Matovina et al. 2018). Among other more often found comorbidities were also migraine found in 6.93%, and hypothyreosis and arrhythmia found in 3.96%. All of our patients (n=7) with migraine were women. It is still unclear whether for most people who have MS and migraines, the migraines came first and are not caused by the MS itself, while some people, however, developed headaches which led to a first brain MRI and eventually to a MS diagnosis. Previous reports suggest even a possible connection to DMTs (Kantor 2012). In

our group of patients with migraine, there was only one patient that was treated with DMT - interferon beta. In regards to abnormalities of heart rhythm it was reported that MS can affect cardiovascular function in a variety of ways leading to abnormalities in blood pressure response, heart rate, heart rhythm, left ventricular systolic function, and may cause pulmonary edema or cardiomyopathy, possibly through brainstem lesions affecting autonomic pathways in the medulla, overall plaque burden, and clinical severity of the disease. Also cardiovascular toxicities of MS therapies, fingolimod and mitoxantrone were also discussed before (Kaplan et al. 2015). Two out of our four patients with arrhythmia, were in treatment with DMT and specifically interferon beta. Connection between MS and thyroid disorders was reported previously, with underlying hypothyroidism usually due to Hashimoto's thyroiditis, which would support the hypothesis of autoimmune pathogenesis for MS (Karni & Abramsky 1999). Previous research showed that gender differences that exist in autoimmunity follow a female bias (Ngo et al. 2014), and this finding was also present in our study. Also, 3.96% of patients had a history of appendectomy. As reported previously there was even a study that found a small but statistically significant and clinically important increased risk for developing multiple sclerosis, in those with tonsillectomy and appendectomy at ≤ 20 years of age (Lunny et al. 2013). Possible underlying factors common to MS and inflammatory conditions requiring surgery like appendicitis and/or a tonsillitis were mentioned as possible connections (Brooks 2013). In our group of patients only one patient had a previous history of tonsillectomy. Since we are talking about small numbers, data should be interpreted with caution.

Limitations of this study include that no additional tools were used like questionnaires, e.g. Patient Health Questionnaire (PHQ) to further assess depressive symptoms (Tobin, 2019). Also, our study did not cover different regions in Croatia, which would maybe provide some additional data in regard to comorbidities affecting patients with MS in Croatia.

CONCLUSIONS

Detection and management of comorbidities in MS is necessary to adequately address them and improve the overall long-term health and outcomes. Comorbidities were found in two-thirds of our patients, with depression most frequent, followed by the hypertension, hyperlipidemia, and migraine. The number of the comorbidities was found to significantly increase with the duration of MS, with women and older patients with MS having significantly more comorbidities. MS patients exactly for this reason require a multidisciplinary approach, that other than neurologists, includes also other subspecialties, like psychiatrists. Patients with

MS also very often have other additional autoimmune disorders, and therefore also require consultation of internal medicine specialists, like immunologists, endocrinologists, and others. Any other comorbidity in MS may also affect the condition of the patient in general, and also their quality of life, and requires a tailored approach in management.

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Contribution of individual authors:

Bošnjak Pašić Marija - conceived and designed the study, collected the data and contributed data or analysis tools, interpretation of the results, approval of the final version

Tudor Katarina Ivana - collected the data and contributed data or analysis tools, first draft, interpretation of the results, approval of the final version

Mustač Filip - collected the data and contributed data or analysis tools

Rajič Fabijan - statistical analyses.

Pašić Hanna - collected the data and contributed data or analysis tools.

Vujević Luka - collected the data and contributed data or analysis tools.

Šarac Helena - interpretation of the results, approval of the final version.

Vidrih Branka - interpretation of the results, approval of the final version.

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Correspondence:

Katarina Ivana Tudor, MD
Department of Neurology, University Hospital Centre Zagreb
Kispaticeva 12, 10 000 Zagreb, Croatia, Croatia
E-mail: katarina.ivana.tudor@kbc-zagreb.hr