



# Multiple sclerosis and autoimmune diseases — a case control study

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## ABSTRACT

**Introduction.** Multiple sclerosis (MS) is one of the most common autoimmune diseases worldwide, and various autoimmune comorbidities have been reported with MS. The aim of this study was to estimate the prevalence of autoimmune disease comorbidity in patients with MS and their relatives in a Polish population.

**Material and methods.** In this retrospective multicentre study, we investigated a group of patients with MS, and their relatives, in terms of age, gender, and the presence of simultaneous autoimmune diseases such as Graves's disease, Hashimoto's thyroiditis, type 1 diabetes mellitus, myasthenia gravis, psoriasis, ulcerative enteritis, Crohn's disease, coeliac disease, rheumatoid arthritis, autoimmune hepatitis and systemic lupus erythematosus.

**Results.** This study included 381 patients with MS, of whom 52.23% were women. 27 patients (7.09%) had at least one autoimmune disease. The most common comorbidity was Hashimoto's thyroiditis (14 patients). 77 patients (21.45%) had relatives with an autoimmune disease, of which the most common was Hashimoto's thyroiditis.

**Conclusions.** Our study revealed that the probability of autoimmune diseases co-occurring in patients with MS, and in their relatives, is higher and we found the greatest risk to be for Hashimoto's thyroiditis.

**Key words:** multiple sclerosis, autoimmune disease, comorbidity, prevalence

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## Introduction

Due to their increasing incidence and chronic nature, autoimmune diseases (AID) pose a growing challenge to modern medicine. Although autoimmune diseases can affect virtually any organ, the tropism to the nervous system, endocrine system, and connective tissue is particularly manifested.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. The disease has three clinical forms: relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS) [1]. There are approximately

2.8 million patients with MS worldwide, mainly in Europe and countries with Caucasian populations i.e. the United States, Australia, and northern Asia [2, 3]. MS is an autoimmune disease that results from complex interactions between genetic and environmental factors. The fact that it shares susceptibility genes with other autoimmune diseases raises the question of whether MS is associated with a higher incidence of these diseases than in the general population. In autoimmune diseases, abnormal humoral and cellular responses to one's own antigens play a role. This can lead to the co-occurrence of different autoimmune diseases in the same patient [4]. As with other

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autoimmune diseases, MS is more common in females, with a peak incidence between the ages of 20 and 40, and there is a tendency to remission during pregnancy and intensification during the postpartum period.

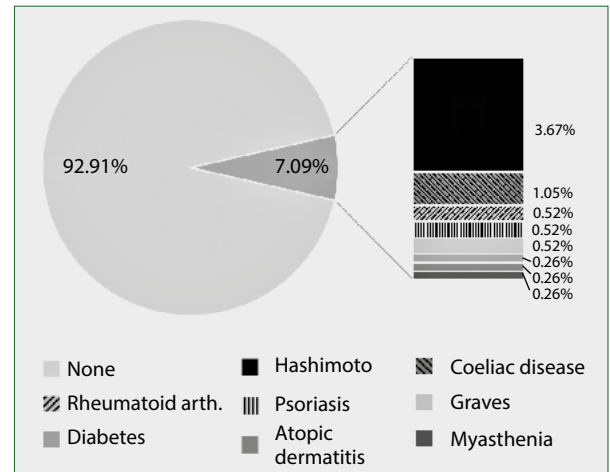
Several studies on this issue have been published, with contradictory results. Some have shown an increased incidence of autoimmune diseases in patients with MS [5, 6], while others claim that these results are related to the more frequent reporting of symptoms by patients with MS [7, 8]. To the best of our knowledge, no study on the co-occurrence of autoimmune diseases in patients with MS and their relatives in a Polish population has yet been published. We hope that the conclusions from this study will draw attention to the problem of the co-occurrence of autoimmune diseases with MS.

## Material and methods

In this retrospective multicentre study, we assessed the prevalence of autoimmune diseases in patients with MS diagnosed according to the 2010 McDonald criteria, and in their relatives. Patients recruited for the study came from Polish MS treatment centres in Bydgoszcz, Białystok, Zabrze, Szczecin and Rzeszów. Expanded Disability Status Score (EDSS) was evaluated by neurostatus-certified neurologists dealing with MS patients on a daily basis. The questionnaire asked about autoimmune diseases such as diabetes, myasthenia gravis, Hashimoto's thyroiditis, Graves's disease, psoriasis, ulcerative enteritis, Crohn's disease, coeliac disease, rheumatoid arthritis, systemic lupus erythematosus, and autoimmune hepatitis both in patients with MS and in their first- and second-line relatives. First-line relatives were defined as the patient's parent, sibling or child, and as such they share c.50% of the patient's genes. Second-line relatives share 25% of a patient's genes and the term encompasses uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings and cousins twice removed.

Each eligible patient was asked to complete a standard questionnaire for the diagnosis of autoimmune diseases.

Statistical analyses were performed with the use of MedCalc (version 15.8). P values less than or equal to 0.05 were considered statistically significant. Data distribution was determined by a d'Agostino-Pearson test. The values were reported as either means  $\pm$  standard deviation (SD) for normally distributed variables or medians with 95% confidence interval (CI) for variables without normal distribution. Fisher's exact test was used to examine associations between sex, presence of AID comorbidity and AID in first- and/or second-line relatives. Clinical characteristics (i.e. age, age at diagnosis, disease duration and EDSS) were checked for mutual correlation with Kendall rank correlation coefficient, then compared between the two sexes and subgroups of patients with and without: comorbid AID, first-line relatives with AID, second-line relatives with AID and first- or second-line relatives with AID. To compare normally distributed variables, a t-test was employed. For non-normal data distribution and



**Figure 1.** Concurrent AID prevalence in study cohort. In study cohort, female patients were more likely to have a concurrent AID (RR = 3.2,  $p = 0.01$ )

ordinal variables, a Mann-Whitney U test was used instead. Subsequently, logistic regression models were calculated, enter and stepwise (significance level to enter the model: 0.10, level to remain: 0.05) to determine the variables with the greatest contribution to the EDSS scores.

This study was approved by the Bioethics Committee of the Nicolaus Copernicus University in Toruń, number KB 438/2017 and all patients signed an informed consent form to participate in the study.

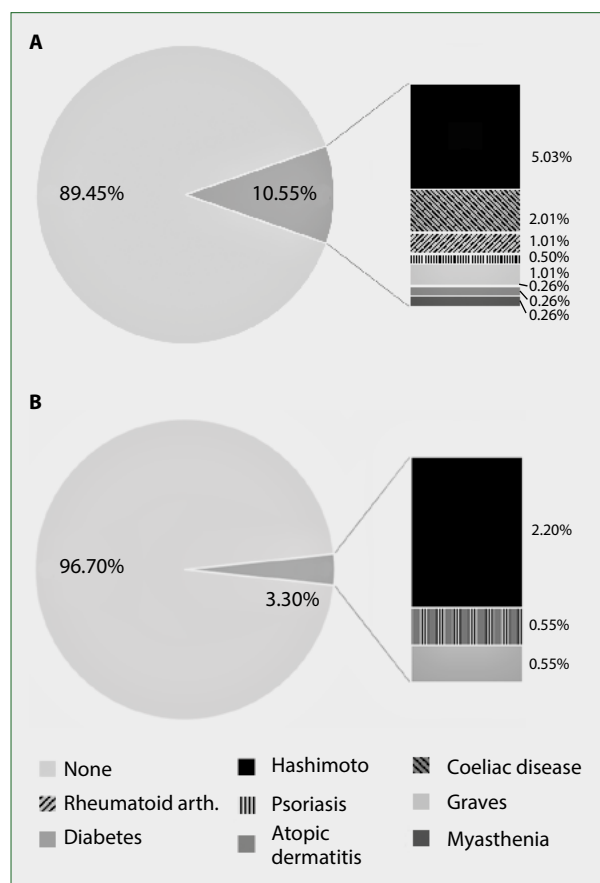
## Results

### Prevalence of AIDs in MS patients and their families

The study involved 381 patients, including 199 females with a mean age of 41.3 years (range: 19–70) and median EDSS of 1.75 (range: 1.5–2.0), and 182 males with a mean age of 40.7 years (range: 21–69) and median EDSS of 2.0 (range: 2.0–2.5). The median disease duration was 8 (range: 7–9) years in males and 6 (range: 5–7) years in females.

Twenty seven patients with MS (7.09%) had at least one additional autoimmune disease: 14 (3.7%) patients had Hashimoto's thyroiditis, four (1.05%) had coeliac disease, two (0.52%) had rheumatoid arthritis, two (0.52%) had psoriasis, two (0.52%) had Graves's disease, one (0.26%) had diabetes type 1, one (0.26%) had atopic dermatitis, and one (0.26%) had myasthenia gravis (Fig. 1).

Seventy seven patients (21.45%) had a family history of AID. Twenty patients (5.17%) had a first- or second-line relative with Hashimoto's thyroiditis, 17 (4.39%) rheumatoid arthritis, 12 (3.10%) type 1 diabetes mellitus, 14 (3.62%) MS, nine (2.33%) psoriasis, seven (1.81%) Graves's disease, and four (1.03%) another autoimmune disease (coeliac disease, colitis ulcerosa, systemic lupus erythematosus, or autoimmune hepatitis) (Fig. 2, 3).



**Figure 2.** A. Concurrent AID prevalence in study cohort, females. B. Concurrent AID prevalence in study cohort, males

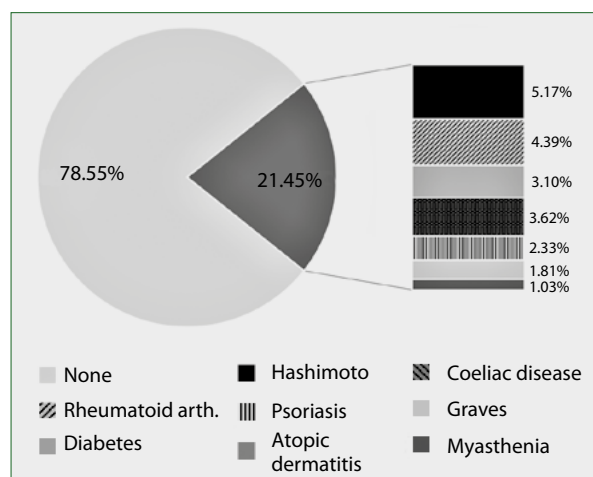
Overall, AIDs in first-line relatives were more than twice as frequent as in second-line relatives (Fig. 4), with the particular exception of MS which was reported in second-line relatives of eight patients (2.11%) but in first-line relatives of only six patients (1.57%). However, recall bias cannot be ruled out. There was no statistically significant association between sex and a family history of AID. Multiple sclerosis patients with first-line relatives affected by AIDs were themselves more likely to have an additional AID [relative risk (RR) = 2.7] ( $p = 0.01$ ).

### Clinical characteristics of MS patients with concurrent AID and family history of AID

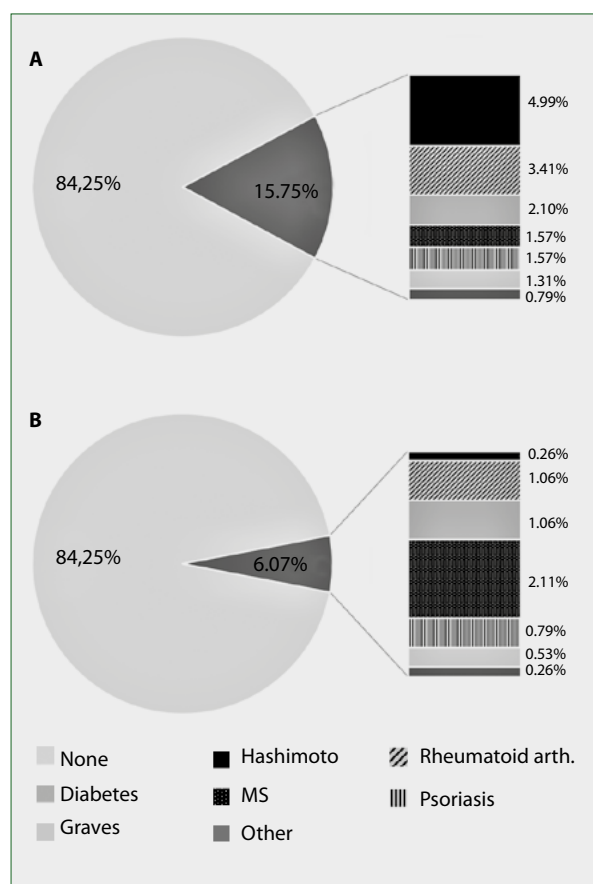
#### Gender

Median EDSS was higher in males than in females [2.0 (95% CI 2.0–2.5) vs. 1.5 (95% CI 1.5–2.0)] ( $p = 0.018$ ), but disease duration was longer in males as well [8(7–9) vs. 6(5–7),  $p = 0.0005$ ]. In the study cohort, disease duration correlated positively with EDSS (Kendall tau: 0.134,  $p = 0.0009$ ), although less than age (Kendall tau: 0.208,  $p < 0.0001$ ) (Fig. 5).

Women did not differ significantly from men in either current age or age at onset of symptoms.



**Figure 3.** AIDs in first- and/or second-line relatives of MS patients



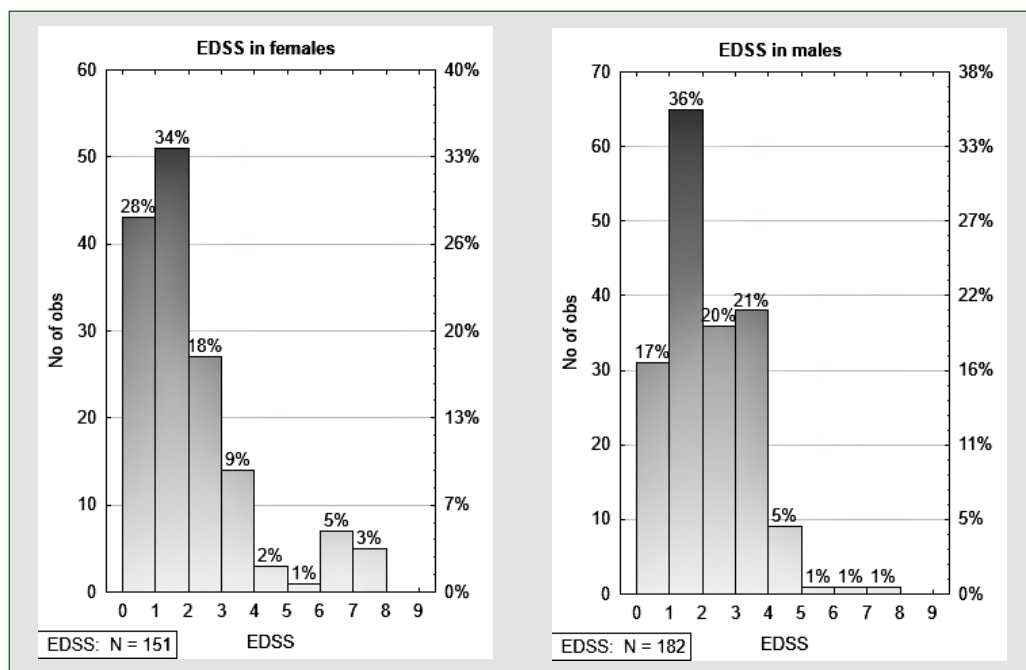
**Figure 4.** A. AIDs in first-line relatives of MS patients. B. AIDs in second-line relatives of MS patients

#### Personal history of concurrent AID

Patients with other AIDs did not differ from those with only MS in terms of EDSS, age, age at onset of symptoms, or disease duration. No gender-specific associations between these characteristics and AIDs were noted (Fig. 2).

**Table 1.** Significant contributors to Expanded Disability Status Score (EDSS) score in logistic regression models

Outcome	Significance level	Variable	Coefficient	Variable p
EDSS $\geq 2$	$< 0.0001$	Sex (♂)	1.2587	$< 0.0001$
		Age	0.0459	0.0014
EDSS $\geq 3$	$< 0.0001$	Sex (♂)	1.5319	$< 0.0001$
		Age	0.0462	0.0020
EDSS $\geq 4$	$< 0.0001$	Sex (♂)	0.9861	0.0404
		Duration	0.1059	0.0026
		Age	0.0520	0.0062
♀ EDSS $\geq 3$	0.0320	Duration	0.1394	0.0391
♀ EDSS $\geq 5$	0.0024	Duration	0.4530	0.0440
♂ EDSS $\geq 2$	0.0197	Age	0.0532	0.0034
♂ EDSS $\geq 3$	0.0061	Age	0.0498	0.0024
♂ EDSS $\geq 4$	0.0005	Age	0.0570	0.0054
		Duration	0.1015	0.0109
♂ EDSS $\geq 5$	0.0258	Age	0.0778	0.0259

**Figure 5.** Expanded Disability Status Score (EDSS) by gender

### Family history of AID

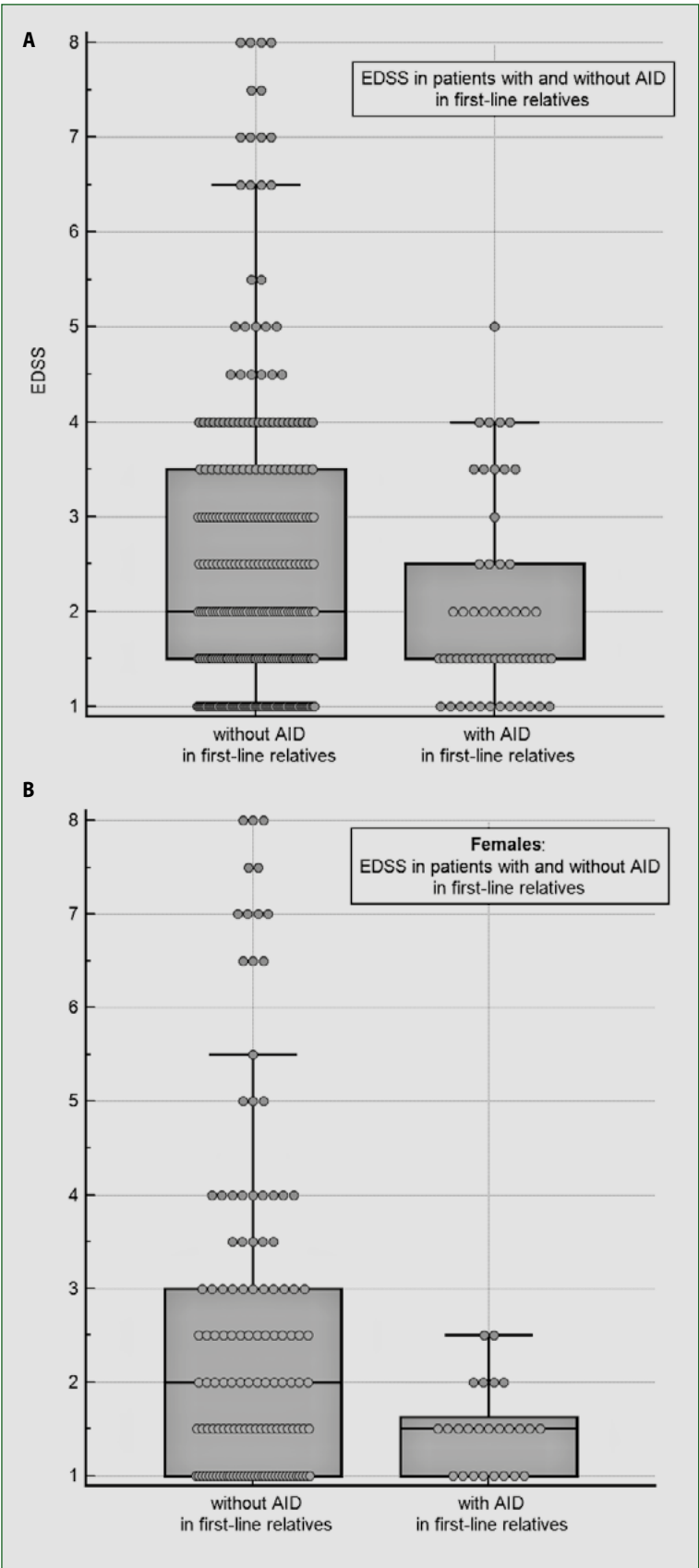
There was no significant difference in age, age at disease onset, or disease duration between patients with and without AID-affected relatives, regardless of the degree of kinship. However, those with a first-line relative with an AID had lower EDSS scores [1.5(1.5–2.0) vs. 2(2.0–2.5),  $p = 0.0346$ ]. This effect was more evident among female patients [1.5(1.07–1.5) vs. 2.0(2.0–2.5),  $p = 0.007$ ] was not present among males (Fig. 6). No similar associations were shown for patients with and without second-line relatives affected by AIDs.

### EDSS predictors in MS patients

In logistic regression analysis, only sex (male), age (older) and disease duration (longer) remained as predictors of EDSS (Tab. 1). On the contrary, no association with additional AID or family history of AID was preserved in the models.

### Discussion

Multiple sclerosis is a chronic disease of the central nervous system that is mainly mediated by T lymphocytes specific



**Figure 6.** A. Expanded Disability Status Score (EDSS) with and without autoimmune disease (AID) in first-line relatives. B. Expanded Disability Status Score (EDSS) with and without autoimmune disease (AID) in first-line relatives

to neuronal antigens. It seems that genetic susceptibility may play a key role here. AIDs may result from the loss of tolerance of one's own tissues. Although the mechanisms underlying impaired tolerance have not been fully understood, deficits in the functioning of regulatory T lymphocytes is one possibility [9]. The coexistence of other AIDs and MS has been described in the literature. But what influence the presence of another AID has on the course of MS is not yet fully understood [10]. It is known that another AID can develop after a diagnosis of MS. And immunomodulatory therapy alone can have an impact on the incidence of other diseases in patients [10–13].

This study assessed the impact of the presence of an additional AID in MS patients and in their first- and second-line relatives on the clinical course of MS. The risk of developing another AID in the studied patients was also assessed.

Our results revealed that patients with MS and without a concomitant AID did not differ in terms of EDSS score compared to those with a concurrent AID. A similar study, carried out on a smaller group of patients, revealed that the mean EDSS was  $1.62 \pm 1.12$  in patients with MS and another AID, compared to the control group, where EDSS was  $3.33 \pm 1.89$  [10]. The authors suggested that MS may coexist with other AIDs, and their presence may modify the course of the disease.

Zéphir et al. [14] presented 66 patients with MS and concomitant enteritis. These patients had a milder course of the disease compared to patients with isolated MS.

These findings reveal that the problem of the coexistence of AIDs is not uncommon, and understanding their development in patients with MS and their relatives could help to better understand the pathomechanisms of AIDs, which may be useful in future prognoses.

Patients who had a first-line or a second-line relative with an AID were more likely to be in the low EDSS group (0–2.5), 80% in the first-line and 78% in the second line, respectively.

As research shows, family history is a frequent contributory factor in a wide variety of autoimmune disorders. Type 1 diabetes may serve as a well-studied example. In more than 14% of patients with type 1 diabetes, at least one first- or second-line relative also suffered from this disease. This shows how important it is to evaluate patients comprehensively and to conduct an in-depth interview on the burden of other diseases in the family [15].

In our study, the presence of an additional AID in patients with MS did not result in more frequent inclusion in the group with low EDSS. However, the presence of such a disease in a first- or second-line relative resulted in a better course of the disease. It is possible that the coexistence of an AID in relatives and patients with MS could predispose them to a milder course of the disease.

A study in Sweden revealed that the relative risk of MS was 1.21 when the parents were diagnosed with any AID. That study was based on a multigenerational registry of diseases. Alleles associated with MS so far do not fully explain the

familial occurrence of MS. On the other hand, the Swedish authors revealed a shared family risk of MS with amyotrophic lateral sclerosis and asthma, which may suggest a common genetic basis [16].

In another publication by authors from Italy, the risk of MS in relatives of patients with MS was 1.9%. The male gender of the affected patient, the female gender of the relative, and the number of family members with an AID, all significantly increased the risk of MS in other relatives. It follows that gender may be of great importance in the risk of developing AID. On the other hand, in our study, there was no correlation between gender and disease progression expressed by belonging to a group with low, medium, and high EDSS.

It seems that establishing similar registries of co-occurring AID and MS in other countries, including Poland, would contribute to the holistic care of patients with MS.

In the presented study, the risk of developing another AID among patients with MS was 10.5%. The greatest risk was found for Hashimoto's thyroiditis. Similarly, patients with type 1 diabetes also have the highest risk of developing Hashimoto's thyroiditis [15].

We observed the least frequent co-occurrence of MS and myasthenia. Danikowski et al. [9] presented possible common mechanisms of the development of these diseases based on the loss of regulatory T lymphocytes. Other AIDs that have been noted have been rheumatoid arthritis, coeliac disease, psoriasis, atopic dermatitis, and Graves's disease. In this study, systemic lupus erythematosus (SLE) was not found in any of the patients although, according to previous studies, it is very often passed on in the family. There is a 10.3 times greater risk of developing SLE among first-degree relatives of patients with SLE. Moreover, regardless of the degree of relationship, people with a family history of SLE have been found to have a greater risk of developing other AIDs, including rheumatoid arthritis, autoimmune thyroid disease, MS, and others [17].

Another study carried out by Fanouriakis et al. [19] showed that patients with concurrent SLE and MS may have mild SLE with mostly dermal, mucosal, and musculoskeletal symptoms. After an average of four years of observation, the authors concluded that the coexistence of these two diseases does not seem to be associated with a severe phenotype of either [18].

There have been few reports on interactions between AIDs, one example being the relationship between colitis and primary sclerosing cholangitis. The coexistence of these diseases is almost always manifested by mild colitis.

On the one hand, the additional burden of another AID is a significant problem for a patient with MS. On the other, it may predict a milder course of the underlying disease.

It is unclear whether the two coexisting AIDs interact with each other. The mechanism of the coexistence itself is difficult to explain [10, 20–22]. It is possible that exposing patients to more antigens may result in greater immune tolerance and a milder course of MS. A more severe activation of regulatory



T lymphocytes and anti-inflammatory cytokines is another hypothesis explaining a milder course of disease in patients with two concurrent AIDs [23–27].

Weiner et al. [28] observed that the progressive course of the disease was more frequent in patients with isolated MS. In the presented study however, patients in the high EDSS group had a comorbid AID more often than not.

This study has several limitations. Firstly, the different forms of MS were not considered separately. Moreover, further research should take into account the immunomodulatory drugs used, because some of the therapies may impair the balance of the immune system and initiate the development of other AIDs [10].

Also, MRI examinations and radiological progression were not compared between patients with and without an additional AID. A clinical evaluation based on EDSS alone may be insufficient.

The analysis of the presence of AIDs among relatives could facilitate the prognostication in patients with MS. It is possible that the coexistence of another disease could improve the prognosis.

Further studies on a larger group of patients are necessary in order to assess the significance of the presented results. In the future, it may be possible to link the analysis of family burdens with the assessment of the presence of specific genes.

A concomitant AID may play a role in the body's tolerance to autoantigens. Further research involving more detail, including MRI and body fluid biomarkers, should be carried out to assess the immune system of patients with MS plus another coexisting AID.

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