Received: 24 June 2024 | Accepted: 2 December 2024

DOI: 10.1111/ene.70019

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Effect of autoimmune comorbidities on multiple sclerosis course: An observational multicenter study

Viviana Nociti[1] | Marina Romozzi[1] | Luca Prosperini[2] | Valentina Torri Clerici[3] | Paolo Ragonese[4] | Antonio Gallo[5] | Giorgia Teresa Maniscalco[6] | Massimiliano Di Filippo[7] | Maria Chiara Buscarinu[8] | Lorena Lorefice[9,10] | Federica Pinardi[11] | Alberto Gajofatto[12] | Paola Cavalla[13] | Fabio Buttari[14] | Diana Ferraro[15] | Giovanna De Luca[16] | Claudio Solaro[17] | Claudio Gasperini[2] | Eleonora Cocco[9,10] | RIREMS Study Group

Correspondence
Viviana Nociti, Multiple Sclerosis Research Center 'Anna Paola Batocchi', Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
Email: viviana.nociti@policlinicogemelli.it

Abstract

Background: The study aims to examine the age and disability levels at diagnosis in people with multiple sclerosis (PwMS), with and without autoimmune comorbidities (AC), and the effect of AC on NEDA-3 status and to characterize AC associated with MS, comparing also therapeutic approaches between MS patients with and without other AC.

Methods: This population-based, multicentric study enrolled patients with relapsing–remitting MS (RRMS) with AC (AC group) or without AC (reference group) from 14 MS centers. Demographical, clinical features, treatment information, MRI activity, EDSS, and no evidence of disease activity (NEDA-3) status were assessed at T36 (enrollment time) and T0 (36 months prior).

Results: Eight hundred seventy-three RRMS patients were included; 215 (24.7%) presented with at least one AC. The AC group was characterized by higher proportion of female patients than reference group ($p = 0.008$). Patients with AC, compared to reference group, exhibited older age at MS onset and MS diagnosis, and higher EDSS score at diagnosis, at T0 (all $p < 0.001$), and T36 ($p = 0.03$). The proportion of patients reaching EDSS 4 was higher in reference group than AC group ($p = 0.03$). People in AC group were more often treated with glatiramer acetate, natalizumab, and rituximab, whereas PwMS from reference group with interferon-beta and fingolimod at T0 and T36. The risk of losing NEDA-3 was lower in AC group (OR = 0.61, 95% CI 0.43–0.86, $p = 0.005$).

Conclusions: AC are common in PwMS and can be related to a delay in onset, diagnosis and higher disability at MS presentation. However, the coexistence of AC is not associated with a worse prognosis.

KEYWORDS
autoimmune, comorbidities, disease-modifying therapies, MS

For affiliations refer to page 7.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, and degenerative demyelinating disease of the central nervous system (CNS) of multifactorial etiology, characterized by broad inter- and intra-individual heterogeneity [1]. The treatment scenario of MS has changed significantly in the past decades due to the growing number of approved disease-modifying therapies (DMTs) [2]. Early diagnosis and intervention are crucial, and a rapid switch to other DTMs is necessary if clinical and magnetic resonance imaging (MRI) measures detect a lack of or suboptimal response [3].

Although the etiology and pathogenesis of MS remain uncertain, it is believed to be an immune-mediated disease characterized by an aberrant immune activation [4]. This hypothesis is also supported by the frequent association of MS with other autoimmune diseases [5]. In fact, MS might share genetic susceptibility and pathogenetic mechanisms with other autoimmune conditions. Nonetheless, multisystem comorbidities are also frequent in people with MS (PwMS), including other neurological disturbances, psychiatric comorbidities, cardiovascular diseases, chronic lung diseases, and metabolic disorders [5–8]. The coexistence of comorbidities has recently engendered significant research interest in the MS field. Many of these comorbidities are present before or at MS symptom onset, but the prevalence seems to increase over time [9]. Given that the MS population has been aging in parallel with increasing general life expectancy, advances in DMTs, and improved health, and that epidemiological studies have shown a growing incidence rate of MS over the past decades, it is expected that the presence of comorbidities will increase the complexity of PwMS management [1]. Several studies have shown that the presence of comorbidities is associated with greater diagnostic delays and increased disability at diagnosis and can affect treatment choices, quality of life (QoL), disability, and mortality [10, 11].

Several studies describe the association between immune-mediated conditions and MS, but the results are still inconsistent. Some studies have suggested that the incidence of autoimmune diseases in individuals with MS may be similar to that of the general population. Conversely, others propose that the prevalence of autoimmune diseases is higher among those with MS when compared to age- and sex-matched control populations [12]. A systematic review of the incidence and prevalence of autoimmune disease in PwMS found that thyroid disease and psoriasis were the most prevalent autoimmune comorbidities (AC). Other findings also support an association of MS with inflammatory bowel disease (IBD), uveitis, pemphigoid [12], and a considerably higher risk of co-occurrence of MS and type 1 diabetes mellitus [13]. Nonetheless, a recent multicentric population-based study found no significant increased risk of autoimmunity among PwMS [14]. Limited information exists regarding the impact of co-existing autoimmune diseases on MS course as well as therapeutic strategies applied to this particular population.

The study aims to examine the age and disability levels at diagnosis in PwMS with and without AC and the effect of AC on NEDA-3 status [3]. Additionally, the study aims to characterize AC associated with MS comparing also therapeutic approaches between MS patients with and without other autoimmune diseases.

METHODS

Design and study population

We conducted a retrospective longitudinal population-based multicentric study involving 14 tertiary MS Centers (Fondazione Policlinico Universitario "Agostino Gemelli," IRCCS, Rome; Istituto Neurologico Carlo Besta, Milan; University of Palermo; University of Campania "Luigi Vanvitelli"; "A. Cardarelli" Hospital, Naples; University of Perugia; Sapienza University of Rome; University of Cagliari; Multiple Sclerosis Rehabilitation, IRCCS, Bologna; University of Verona; University Hospital, Turin; IRCCS Neuromed, Pozzilli; SS. Annunziata University Hospital, Chieti; Azienda Ospedaliero-Universitaria di Modena). We consecutively enrolled patients diagnosed with relapsing–remitting MS (RRMS) according to McDonald 2017 criteria [15], with a disease duration ≤10 years from the onset of MS symptoms, with or without concomitant AC, aged >18 years old. Patients were enrolled from July 1, 2019, to January 31, 2020.

Inclusion criteria for PwMS with concomitant AC (AC group) were as follows: patients diagnosed with one or more autoimmune diseases (diagnosed before or simultaneously with MS diagnosis) who were not undergoing treatment with immunosuppressive or monoclonal drugs for the autoimmune disease because not indicated or not necessary (e.g., type I diabetes, thyroiditis, coeliac disease, and psoriasis) and an available 36-month follow-up (retrospective from the time of the visit).

Exclusion criteria were as follows: PwMS with one or more autoimmune diseases diagnosed after MS diagnosis and the initiation of treatment in order to exclude diseases caused by DMTs (e.g., interferon-beta and alemtuzumab), the presence of other comorbidities including other neurological conditions (i.e., cerebrovascular and neurodegenerative diseases), unavailability, or incomplete brain MRI data.

All PwRRMS with the same follow-up and without AC were enrolled as a reference group.

The period of observation for each patient was considered from T36 (time of observation and, therefore, of enrollment) (last follow-up available) and T0 (retrospective data corresponding to 36 months prior) to the last registered appointment.

Patients' demographic and clinical information

The following demographic and clinical information was collected at baseline (T36) by a consultant neurologist who was qualified to perform the Expanded Disability Status Scale (EDSS) assessments according to the standardized scoring system of the Neurostatus

(http://www.neurostatus.net/scoring/index.php): age, gender, age at onset, age at diagnosis, the occurrence of clinical relapses, measures of MRI activity, EDSS scores at the time of diagnosis, at the time of enrollment (T36) and T0, type of DMT (classified as first and second line DMTs [17]) at T36 and T0 and the reason for discontinuation in case of DMT interruption.

The requirement for inclusion of patients' brain MRI was magnet strengths of at least 1.5 Tesla (1.5 T), and as per guidelines, the following sequences were considered mandatory: axial proton density or T2-weighted/T2-weighted fluid-attenuated inversion recovery (FLAIR) spin echo or turbo spin echo, sagittal two-dimensional (2D) or three-dimensional (3D) T2-FLAIR and axial 2D or 3D post-contrast T1-weighted spin echo or turbo spin echo [16]. The brain MRI scans at T36 were acquired for each patient in a situation of clinical stability (i.e., a minimum of 3 months after the last clinical relapse/steroid treatment and a minimum of 6 months from the initiation of a DMT). Disability worsening was considered when the EDSS score was increased by 1 point if the baseline EDSS score was <5.0, or 0.5 points if the baseline EDSS score was ≥5.5, confirmed over 6 months. The NEDA-3 status was defined as no evidence of (1) relapses, (2) disability progression, or (3) MRI activity, that is, new or enlarging T2 and/or T1 gadolinium-enhancing lesions [18].

The information on the concomitant AC was obtained by consulting the patients' medical records. The ACs were classified according to the International Classification of Diseases (ICD), 11th edition. Autoimmune diseases were further classified according to the location of the autoimmune involvement into organ-specific or systemic depending on whether the autoimmune response is directed against a particular tissue or against widespread antigens as in chronic inflammatory autoimmune diseases [19]. The study was approved by the Ethical Committee "Università Cattolica Sacro Cuore" in Rome, Italy.

Statistical Analysis

Statistical data were analyzed using SPSS version 21.0 and Microsoft Office Excel (Microsoft, Redmond, Washington, USA). Summary statistics were reported as mean (± standard deviation, SD) or median for continuous variables and as frequencies and percentages for categorical variables. Clinical data were compared using the two-tailed Fisher's exact test for categorical variables. Data normality was assessed using the Shapiro–Wilk test. In the case of normal distribution, a two-tailed Student *t*-test was performed to compare the two groups. In the case of non-normal data distribution, the Mann–Whitney test was employed. Heterogeneity across the Rising Italian Researchers in Multiple Sclerosis (RIREMS) sites was assessed after grouping sites that enrolled a number of patients <5% of the total. We evaluated the effect of AC on NEDA status (outcome of interest), and its subcomponents (relapse, MRI activity, and disability worsening), in univariable analyses and multivariable logistic regression models, including as covariates of no interest: sex, age, disease duration, EDSS score, DMT class, and site. Two-sided *p* values <0.05 were considered significant.

RESULTS

Patients characteristics

A total of 873 RRMS patients were included. Among these patients, 215 (24.7%) presented with at least one concomitant immune-mediated disease, while 658 PwRRMS, free from immune-mediated diseases, constituted the reference group. The AC group was characterized by a higher proportion of female patients, with 77.7% females in the AC group compared to 67.8% in the reference group ($p=0.008$) (Table 1).

Among the 215 patients with concomitant immune-mediated diseases, 223 autoimmune comorbidities were identified (190 organ-specific and 33 systemic). The most prevalent AC within this group was thyroid gland-related autoimmunity, representing 52.9% of all autoimmune comorbidities and comprising Hashimoto thyroiditis ($n=113$) and Basedow disease ($n=5$). Other autoimmune comorbidities included diabetes mellitus type 1 (8.5%), coeliac disease (3.6%), IBD (6.3%), and rheumatoid arthritis (6.7%) (all the autoimmune comorbidities are summarized in Table 2).

Patients with concomitant AC exhibited an older age at MS onset (34.8 ± 10.5) compared to the reference group (31.1 ± 10.3) ($p<0.001$), as well as an older age at the time of MS diagnosis (37.1 ± 10.6) compared to the reference group (33.0 ± 10.6) ($p<0.001$) (Table 1).

Additionally, the AC group displayed significantly higher scores on the EDSS in comparison with the reference group at the time of MS diagnosis ($p<0.001$), at T0 ($p<0.001$), and the last available follow-up (T36) ($p=0.031$) (Table 1). The proportion of patients reaching the EDSS 4 milestone was overall higher in the reference group than in the AC group ($p=0.026$). No significant difference was observed for the EDSS 6 milestone.

There was heterogeneity across centers in baseline patients' characteristics (all *p* values <0.05), including proportions of case and controls, age at onset and diagnosis, time elapsed between onset and diagnosis, EDSS score (Supplementary Table) as well as in the explored outcomes, with except for treatments received and reasons for switching treatments. This heterogeneity was accounted for by including in the univariable and multivariable analysis a term which indicates centers.

Disease-modifying therapies

Disease-modifying therapies in the AC and reference groups (at T0 and T36) are summarized in Table 3. People with MS and concomitant AC were more often treated with glatiramer acetate, natalizumab, and rituximab, whereas PwMS from the reference group were more often treated with interferon-beta and fingolimod at T0 and T36.

TABLE 1 Characteristics of the cohort of people with multiple sclerosis.

	AC group ($n=215$)	Reference group ($n=658$)	p-value
Sex, *n* (%)			
Men	48 (22.3)	212 (32.2)	**0.008**
Women	167 (77.7)	446 (67.8)	
Age at onset, years			
Mean (SD)	34.8 (10.5)	31.1 (10.3)	**<0.001**
Median [interval]	35.3 [7.6–58.6]	30.0 [9.3–71.4]	
Age at diagnosis, years			
Mean (SD)	37.1 (10.6)	33.0 (10.6)	**<0.001**
Median [interval]	37.1 [7.9–62.4]	31.8 [9.8–72.2]	
Time elapsed between onset and diagnosis, years			
Mean (SD)	2.3 (4.4)	1.9 (3.5)	0.402
Median [interval]	0.5 [<0.1–33.0]	0.6 [<0.1–30.8]	
Disease duration, years			
Mean (SD)	9.4 (6.9)	7.2 (4.6)	**<0.001**
Median [interval]	7.4 [0.7–40.6]	6.1 [1.3–26.8]	
EDSS at diagnosis			
Mean (SD)	1.7 (1.1)	1.0 (0.9)	**<0.001**
Median [interval]	1.5 [0–6.0]	1.0 [0–6.0]	
EDSS at T0			
Mean (SD)	2.0 (1.2)	1.5 (1.2)	**<0.001**
Median [interval]	2.0 [0–6.5]	1.0 [0–6.5]	
EDSS at T36			
Mean (SD)	2.3 (1.5)	2.1 (1.4)	**0.03**
Median [interval]	2.0 [0–7.0]	2.0 [0–7.0]	
Patients with EDSS score ≥4.0 at T0, *n* (%)	22 (10.2)	46 (7.0)	0.164
Patients with EDSS score ≥4.0 at T36, *n* (%)	37 (17.2)	73 (11.1)	**0.026**
Patients with EDSS score ≥6.0 at T0, *n* (%)	4 (1.9)	8 (1.2)	0.713
Patients with EDSS score ≥6.0 at T36, *n* (%)	8 (3.7)	26 (4.0)	0.879
Relapses during follow-up (T0-T36), *n* (%)	44 (20.5)	107 (16.3)	0.19
Disability progression during follow-up (T0-T36), *n* (%)	37 (17.2)	211 (32.1)	**<0.001**
MRI activity during follow-up (T0-T36), *n* (%)	48 (22.3)	130 (19.8)	0.475
Any disease activity during follow-up (T0-T36), *n* (%)	87 (40.5)	322 (48.9)	**0.034**

Abbreviations: AC, autoimmune comorbidities; EDSS, Expanded Disability Status Scale; MRI: magnetic resonance imaging; SD, standard deviation.
Bold values indicate statistical significance.

There were no differences in terms of DMT prescription between patients with organ-specific and systemic autoimmunity (as T0 and T36), with the only exception of glatiramer acetate, which was more often prescribed in those with organ-specific autoimmunity than in those with systemic autoimmunity ($p<0.05$).

At the T0 evaluation, treatment discontinuation due to poor tolerability occurred more often in AC than in the reference group ($p<0.05$). Among the AC group, three patients discontinued glatiramer acetate, and two discontinued teriflunomide. In the reference group, all three patients who discontinued DMT were on teriflunomide.

At T36 evaluation, treatment discontinuation due to lack of efficacy occurred more often in the AC group than in the reference group ($p<0.05$) (Table 4). Within cases, there was no difference in reasons for discontinuation between organ-specific and systemic autoimmune diseases.

Impact of autoimmune comorbidities on disease activity (NEDA-3)

The risk of losing NEDA-3 was lower in AC than in the reference group: unadjusted odds ratio (OR) = 0.71, 95% confidence interval (CI) 0.52 to 0.97 ($p=0.03$); adjusted OR = 0.57, 95% CI 0.40 to 0.80 ($p=0.001$). This feature was mainly driven by disability accrual

TABLE 2 Prevalence and type of autoimmune comorbidities in people with multiple sclerosis.

	n	%
Organ-specific autoimmunity	190	85.2
Thyroid gland	118	52.9
Hashimoto thyroiditis	113	
Basedow disease	5	
Digestive tract and accessory organs	39	17.5
Diabetes mellitus type 1	19	
Coeliac disease	8	
Ulcerative colitis	6	
Crohn disease	4	
Hepatitis	2	
Skin and appendages	24	10.8
Psoriasis[a]	16	
Vitiligo	4	
Lichen planus	1	
Others	9	4
Uveitis	4	
Thrombocytopenia	3	
Myasthenia	1	
Pernicious anemia	1	
Systemic autoimmunity	33	14.8
Rheumatoid arthritis	15	
Connectivitis	7	
Antiphospholipid syndrome	3	
Raynaud syndrome	3	
Sjogren syndrome	3	
Systemic sclerosis	2	

[a]Three patients with psoriasis also had psoriatic arthritis.

events, which occurred more often in PwMS in the reference group than in the AC group (unadjusted OR = 0.51, 95% CI 0.34 to 0.75, $p < 0.001$; adjusted OR = 0.49, 95% CI 0.29 to 0.70, $p < 0.001$). There were no between-group differences on relapses (unadjusted OR = 1.32, 95% CI 0.90 to 1.96, $p = 0.190$; adjusted OR = 1.28, 95% CI 0.82 to 2.01, $p = 0.273$) and MRI activity (unadjusted OR = 0.86, 95% CI 0.59 to 1.24, $p = 0.475$; adjusted OR = 0.99, 95% CI 0.65 to 1.50, $p = 0.955$) (Figure 1).

Among AC PwMS, the risk of losing NEDA-3 was lower in patients with organ-specific than in those with systemic AC (unadjusted OR = 0.57, 95% CI 0.30 to 1.06, $p = 0.07$; adjusted OR = 0.43, 95% CI 0.20 to 0.92, $p = 0.03$). This feature was mainly driven by relapse events, which occurred more often in patients with systemic AC than in those with organ-specific AC other than thyroid autoimmunity (annualized relapse rate at follow-up 1.14 vs. 0.06, $p = 0.004$). In more detail, the risk of losing NEDA-3 was even lower in patients with autoimmune thyroid disorders (unadjusted OR = 0.72, 95% CI 0.51 to 1.03, $p = 0.07$; adjusted OR = 0.52, 95% CI 0.27 to 1.01, $p = 0.06$).

DISCUSSION

The association between MS and comorbidities has garnered increasing interest as a potential factor that may contribute to disease variability and outcome. Thus far, comorbid conditions have been shown to influence the timing of diagnosis, the disease course and disability progression, QoL, treatment decisions, and mortality [20–22]. The presence of shared pathways and the involvement of similar immune cell types in the pathogenesis of AC may underlie the risk of both MS and other autoimmune pathologies [23].

In this multicenter observational study, 215 (24.7%) people with RRMS presented with at least one concomitant immune-mediated disease, with thyroid autoimmunity being the most common condition. The prevalence of comorbid autoimmune conditions among PwMS was marginally higher than the range reported in the existing literature, which spans from 3% to 26.1% [12], but this could be due to the study design and enrollment criteria. As expected, PwMS with AC were more skewed toward female gender than MS. Furthermore, PwMS with AC tended to be older both at MS onset and at MS diagnosis compared to those in the reference group and exhibited higher disability scores at the time of diagnosis compared to the reference group. Our data are in line with those reported by Marrie et al. in the study using the North American Research Committee on Multiple Sclerosis Registry, showing an association between comorbidities and severity of disability at MS diagnosis [10]. On the contrary, we did not find a diagnostic delay from the onset of MS symptoms but an older age at the MS onset in the AC group. An explanation of these data could be the erroneous interpretation of the MS prodromal symptoms, mistakenly attributed by patients to the preexisting AC condition, thus delaying the identification of MS onset and consequently the MS diagnosis, also favoring a higher disability degree at diagnosis.

Even if the AC group displayed significantly higher scores on the EDSS in comparison with the reference group at T0 and T36, the proportion of patients reaching the EDSS 4 milestone was overall higher in the reference group than in cases. Moreover, the risk of losing NEDA-3 was lower in the AC group than in PwMS from the reference group. This difference was primarily driven by disability accrual events in the reference group compared to the AC group. The higher frequency of high-efficacy DMTs in the AC group, compared to the reference population, may provide an explanation for the greater number of patients in the reference group experiencing disability progression, resulting in the loss of NEDA-3 status. We also have to consider the impact of an autoimmune comorbid disease on the MS course, which has not been fully clarified. The coexistence of another immune-mediated condition may reduce the possibility of disability progression due to unknown changes in immunological pathways that may increase the tolerance against autoantigens. This notion finds support in a study involving a small cohort of PwMS with concurrent AC, in which these patients had less disability compared to those with isolated MS [24]. Similar

TABLE 3 Types of disease-modifying therapies (DMTs) in the two cohorts of people with multiple sclerosis at T36 (enrollment time) and T0 (36 months prior).

	T0		T36	
	AC group ($n = 215$)	Reference group ($n = 658$)	AC group ($n = 215$)	Reference group ($n = 658$)
	Mean (SD)		Mean (SD)	
Glatiramer acetate	72 (33.5)	92 (14.0)[a]	55 (25.5)	73 (11.1)[a]
Dimethyl fumarate	57 (26.5)	203 (30.9)	60 (27.9)	191 (29.0)
Interferon-beta	22 (10.2)	175 (26.6)[a]	19 (8.8)	169 (25.7)[a]
Natalizumab	19 (8.8)	0 (0)[a]	22 (10.2)	14 (2.1)[a]
Teriflunomide	15 (7.0)	28 (4.3)[a]	15 (7.0)	31 (4.7)[a]
Rituximab	11 (5.1)	0 (0)[a]	11 (5.1)	0 (0)[a]
Fingolimod	10 (4.7)	122 (18.5)[a]	15 (7.0)	108 (16.4)[a]
Alemtuzumab	5 (2.3)	28 (4.3)[a]	5 (2.3)	28 (4.3)
Cladribine	0 (0)	0 (0)	3 (1.4)	5 (0.8)
Ocrelizumab	0 (0)	0 (0)	6 (2.8)	36 (5.5)
No therapy	4 (1.9)	10 (1.5)	4 (1.9)	3 (0.5)

Abbreviations: AC, autoimmune comorbidities; SD, standard deviation.

[a]Refers to statistically significant results at a two-sided p-value <0.05.

TABLE 4 Reason for discontinuation of disease-modifying therapies (DMTs) in the two cohorts of people with multiple sclerosis at T36 (enrollment time) and T0 (36 months prior).

	T0		T36	
	AC group ($n = 215$)	Reference group ($n = 658$)	AC group ($n = 215$)	Reference group ($n = 658$)
	n (%)		*n* (%)	
No interruption	197 (91.6)	602 (91.6)	179 (83.3)	579 (88.0)
Lack of efficacy	13 (6.0)	16 (2.5)[a]	25 (11.6)	55 (8.4)
Poor tolerability	1 (0.5)	5 (0.8)[a]	5 (2.3)	3 (0.5)[a]
Loss of adherence	0 (0)	24 (3.7)[a]	2 (0.5)	2 (0.3)
Pregnancy	0 (0)	2 (0.3)	1 (0.5)	5 (0.8)
Others (unspecified)	0 (0)	2 (0.3)	0 (0)	4 (1.9)
No treatment	4 (1.9)	0 (0)	4 (1.9)	10 (1.5)

Abbreviation: AC, autoimmune comorbidities.

[a]Refers to statistically significant results.

findings were reported in a study on PwMS with concomitant IBD that showed that they exhibited a milder course of the disease than patients with MS alone and in a study on nine patients with both systemic lupus erythematosus and MS [25, 26]. Lastly, in a study by Sovetkina et al. PwMS patients who develop autoimmune thyroid disease had a better response to alemtuzumab, as demonstrated by a reduced disability and a lower relapse rate [27].

However, several other evidence showed that AC in patients with MS are associated with more severe MR imaging outcomes related to demyelination and neurodegeneration [28, 29].

In our study, there were no substantial differences in terms of DMTs taken between patients with organ-specific and systemic autoimmunity, but among the patients with AC, the risk of losing NEDA-3 was lower in patients with organ-specific than in those with systemic autoimmune conditions, mainly due to relapse events occurring more often in patients with systemic AC. These findings are also in line with previous studies on MS and rheumatoid arthritis (a systemic AC), in which rheumatoid arthritis was associated with a more than threefold increased risk of relapses [30]. We might speculate that in systemic AC, there is a more widespread increase in the levels of various cytokines, which might also influence the permeability of the blood–brain barrier [31, 32]. However, these findings must be interpreted with caution due to the limited number of participants in our study who reported having systemic autoimmune conditions. The strength of the study lies in its well-defined cohort, comprised exclusively of individuals with RRMS, and the 3-year longitudinal design. However, it is essential to acknowledge certain limitations. Firstly, data were retrospectively

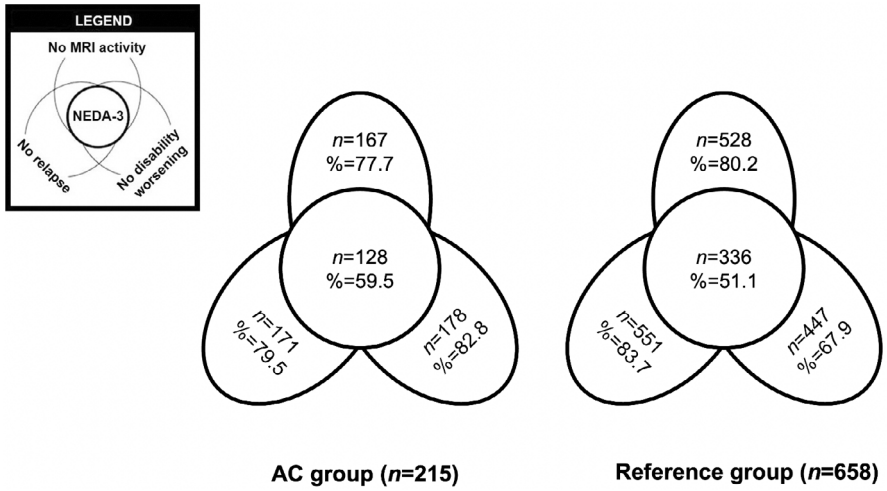

FIGURE 1 Impact of autoimmune comorbidities on disease activity (NEDA-3).

collected from electronic records and we did not thoroughly investigate the time window between the onset/diagnosis of MS and the onset of concurrent AC. Additionally, although the multicentric study provides a more representative and larger sample, the heterogeneity across centers in baseline patient characteristics and outcomes may affect the generalizability of the findings.

Lastly, the exclusion of PwMS who were not undergoing treatment with immunosuppressive or monoclonal antibodies for their autoimmune disease due to the absence of indications or necessity may have introduced a bias by excluding patients with more severe forms of AC. In conclusion, our study underscores the relevance of autoimmune comorbidities associated with RRMS and their potential impact on diagnostic delay, disability, disease activities, and treatment strategies. An important aspect to consider in future research is the identification of the pathogenetic connections between MS and other AC, with potential relevant consequences on management and treatment strategies.

AUTHOR CONTRIBUTIONS

Viviana Nociti: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; software; project administration; formal analysis; data curation; supervision; resources. **Marina Romozzi:** Writing – original draft; methodology; writing – review and editing. **Luca Prosperini:** Conceptualization; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing; formal analysis; software; data curation. **Valentina Torri Clerici:** Conceptualization; investigation. **Paolo Ragonese:** Conceptualization; investigation. **Antonio Gallo:** Conceptualization; investigation. **Giorgia Teresa Maniscalco:** Conceptualization; investigation. **Massimiliano Di Filippo:** Conceptualization; investigation. **Maria Chiara Buscarinu:** Conceptualization; investigation. **Lorena Lorefice:** Conceptualization; investigation. **Federica Pinardi:** Conceptualization; investigation. **Alberto Gajofatto:** Conceptualization; investigation. **Paola Cavalla:** Conceptualization; investigation. **Fabio Buttari:** Conceptualization; investigation. **Diana Ferraro:** Conceptualization; investigation. **Giovanna De Luca:** Conceptualization; investigation. **Claudio Solaro:** Conceptualization; investigation. **Claudio Gasperini:** Conceptualization; investigation. **Eleonora Cocco:** Conceptualization; investigation.

AFFILIATIONS

[1]Multiple Sclerosis Research Center 'Anna Paola Batocchi', Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[2]Multiple Sclerosis Center, Neurology Unit S. Camillo-Forlanini Hospital, Rome, Italy
[3]Neuroimmunology and Neuromuscular Diseases Unit, Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milan, Italy
[4]Department of Biomedicine, Neurosciences and advanced Diagnostics, University of Palermo, Palermo, Italy
[5]Department of Advanced Medical and Surgical Sciences (DAMSS), University of Campania "Luigi Vanvitelli", Caserta, Italy
[6]Neurological Clinic-Stroke Unit and Multiple Sclerosis Center, "A. Cardarelli" Hospital, Naples, Italy
[7]Section of Neurology, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[8]Centre for Experimental Neurological Therapies (CENTERS), Department of Neurosciences, Mental Health and Sensory Organs, Sapienza University of Rome, Rome, Italy
[9]Multiple Sclerosis Center, Binaghi Hospital, Cagliari, Italy
[10]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[11]IRCCS Istituto delle scienze neurologiche di Bologna, UOSI Riabilitazione Sclerosi Multipla, Bologna, Italy
[12]Dipartimento di Neuroscienze, Biomedicina e Movimento, Università di Verona, Verona, Italy
[13]Multiple Sclerosis Center, University Neurology Unit 1, Department of Neurosciences and Mental Health, AOU City of Health & Science University Hospital, Turin, Italy
[14]Unit of Neurology & Neurorehabilitation, IRCCS Neuromed, Pozzilli, Italy
[15]Neurology Unit, Ospedale Civile di Baggiovara, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy
[16]MS Centre, Neurology Unit, SS. Annunziata University Hospital, Chieti, Italy
[17]Rehabilitation Department, Mons. L. Novarese, Vercelli, Italy

FUNDING INFORMATION

This study was not supported by any sponsor or funder.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare related to this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ORCID

Viviana Nociti https://orcid.org/0000-0002-4607-3948
Marina Romozzi https://orcid.org/0000-0001-6016-3141
Luca Prosperini https://orcid.org/0000-0003-3237-6267
Paolo Ragonese https://orcid.org/0000-0003-2516-1567
Antonio Gallo https://orcid.org/0000-0002-2203-6237
Massimiliano Di Filippo https://orcid.org/0000-0002-2645-7477
Lorena Lorefice https://orcid.org/0000-0003-2050-2908
Diana Ferraro https://orcid.org/0000-0003-4818-3806
Claudio Solaro https://orcid.org/0000-0001-6167-3987
Claudio Gasperini https://orcid.org/0000-0002-3959-4067

REFERENCES

1. Dobson R, Giovannoni G. Multiple sclerosis—a review. *Eur J Neurol*. 2019;26(1):27-40.
2. Kalincik T, Diouf I, Sharmin S, et al. Effect of disease-modifying therapy on disability in relapsing-remitting multiple sclerosis over 15 years. *Neurology*. 2021;96(5):e783-e797.
3. Giovannoni G, Tomic D, Bright JR, Havrdová E. "No evident disease activity": the use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler*. 2017;23(9):1179-1187.
4. Naegele M, Martin R. The good and the bad of neuroinflammation in multiple sclerosis. *Handb Clin Neurol*. 2014;122:59-87.
5. Nociti V, Romozzi M. Multiple sclerosis and autoimmune comorbidities. *J Pers Med*. 2022;12(11):1828.
6. Magyari M, Sorensen PS. Comorbidity in multiple sclerosis. *Front Neurol*. 2020;11:851.
7. Hauer L, Perneczky J, Sellner J. A global view of comorbidity in multiple sclerosis: a systematic review with a focus on regional differences, methodology, and clinical implications. *J Neurol*. 2021;268(11):4066-4077.
8. Nociti V, Romozzi M. The importance of managing modifiable comorbidities in people with multiple sclerosis: a narrative review. *J Pers Med*. 2023;13(11):1524.
9. Lo LMP, Taylor BV, Winzenberg T, Palmer AJ, Blizzard L, van der Mei I. Change and onset-type differences in the prevalence of comorbidities in people with multiple sclerosis. *J Neurol*. 2021;268(2):602-612.
10. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity delays diagnosis and increases disability at diagnosis in MS. *Neurology*. 2009;72(2):117-124.
11. Marrie RA. Comorbidity in multiple sclerosis: implications for patient care. *Nat Rev Neurol*. 2017;13(6):375-382.
12. Marrie RA, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. *Mult Scler*. 2015;21(3):282-293.
13. Bechtold S, Blaschek A, Raile K, et al. Higher relative risk for multiple sclerosis in a pediatric and adolescent diabetic population: analysis from DPV database. *Diabetes Care*. 2014;37(1):96-101.
14. Ramagopalan SV, Dyment DA, Valdar W, et al. Autoimmune disease in families with multiple sclerosis: a population-based study. *Lancet Neurol*. 2007;6(7):604-610.
15. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.
16. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol*. 2016;15(3):292-303.
17. Ingwersen J, Aktas O, Hartung HP. Advances in and algorithms for the treatment of relapsing-remitting multiple sclerosis. *Neurotherapeutics*. 2016;13(1):47-57.
18. Hegen H, Bsteh G, Berger T. 'No evidence of disease activity'—is it an appropriate surrogate in multiple sclerosis? *Eur J Neurol*. 2018;25(9):1107.
19. Boitard C. Pathophysiology of autoimmune diseases. *Klin Wochenschr*. 1990;68(Suppl 21):1-9.
20. Berrigan LI, Fisk JD, Patten SB, et al. Health-related quality of life in multiple sclerosis: direct and indirect effects of comorbidity. *Neurology*. 2016;86(15):1417-1424.
21. Salter A, Tyry T, Wang G, Fox RJ, Cutter G, Marrie RA. Examining the joint effect of disability, health behaviors, and comorbidity on mortality in MS. *Neurol Clin Pract*. 2016;6(5):397-408.
22. Newland PK, Lorenz R, Budhathoki C, Jensen MP. The presence of symptoms with comorbid conditions in individuals with multiple sclerosis (MS). *Clin Nurs Res*. 2016;25(5):532-548.
23. Baranzini SE. The genetics of autoimmune diseases: a networked perspective. *Curr Opin Immunol*. 2009;21(6):596-605.
24. Sahraian MA, Owji M, Naser Moghadasi A. Concomitant multiple sclerosis and another autoimmune disease: does the clinical course change? *Clin Neurol Neurosurg*. 2016;150:92-95.
25. Zéphir H, Gower-Rousseau C, Salleron J, et al. Milder multiple sclerosis course in patients with concomitant inflammatory bowel disease. *Mult Scler*. 2014;20(8):1135-1139.
26. Fanouriakis A, Mastorodemos V, Pamfil C, et al. Coexistence of systemic lupus erythematosus and multiple sclerosis: prevalence, clinical characteristics, and natural history. *Semin Arthritis Rheum*. 2014;43(6):751-758.
27. Sovetkina A, Nadir R, Scalfari A, et al. Development of autoimmune thyroid disease in multiple sclerosis patients post-Alemtuzumab improves treatment response. *J Clin Endocrinol Metab*. 2020;105(9):e3392-e3399.
28. Zivadinov R, Raj B, Ramanathan M, et al. Autoimmune comorbidities are associated with brain injury in multiple sclerosis. *AJNR Am J Neuroradiol*. 2016;37(6):1010-1016.
29. Lorefice L, Fenu G, Pitzalis R, et al. Autoimmune comorbidities in multiple sclerosis: what is the influence on brain volumes? A Case-Control MRI Study. *J Neurol*. 2018;265(5):1096-1101.
30. Tettey P, Siejka D, Simpson S Jr, et al. Frequency of comorbidities and their association with clinical disability and relapse in multiple sclerosis. *Neuroepidemiology*. 2016;46(2):106-113.
31. Moudgil KD, Choubey D. Cytokines in autoimmunity: role in induction, regulation, and treatment. *J Interf Cytokine Res*. 2011;31(10):695-703.
32. Yang J, Ran M, Li H, et al. New insight into neurological degeneration: inflammatory cytokines and blood–brain barrier. *Front Mol Neurosci*. 2022;15:1013933.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nociti V, Romozzi M, Prosperini L, et al. Effect of autoimmune comorbidities on multiple sclerosis course: An observational multicenter study. *Eur J Neurol*. 2025;32:e70019. doi:10.1111/ene.70019