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Clinical features of Sjogren's syndrome in patients with multiple sclerosis

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Objectives – To assess the frequency of clinical features of Sjogren's syndrome (SS) in patients with multiple sclerosis (MS) receiving treatment with disease-modifying drugs (DMDs) or naïve to treatment and the possible association with clinical, cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) parameters. *Methods* – A multicentre cross-sectional observational study was designed, based on a structured neurologist-administered questionnaire to 440 patients. *Results* – Twenty-eight of 230 (12%) patients receiving treatment with DMDs ($DMDs^+$) and 14 of 210 (6.6%) treatment-naïve patients ($DMDs^-$) showed clinical features of SS. Four primary SS were diagnosed, two of which were $DMDs^+$ and two were $DMDs^-$. Sicca symptoms were significantly associated with higher EDSS scores ($P = 0.018$), a low frequency of gadolinium-enhanced MRI-positive lesions ($P = 0.018$) and cerebral disturbances ($P = 0.001$). *Conclusions* – Screening for the clinical features of SS should be performed in patients with MS both receiving treatment with immunomodulatory drugs and without therapy.

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Key words: Multiple sclerosis; Sjogren's syndrome; immunomodulatory therapies; interferon beta; glatiramer acetate

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Introduction

Primary Sjogren's syndrome (PSS) may coexist with multiple sclerosis (MS), but its real prevalence is disputed ranging from 0% to 3.3% (1–3) This controversy arises from the fact that SS may mimic clinical and magnetic resonance imaging (MRI) findings of MS (4, 5) and that the detection of specific serum autoantibodies may sometimes be negative (1, 5). The features of PSS may appear before or several years after the onset of MS (1, 4). However, the criteria used to diagnose PSS are heterogeneous, and only limited cohorts of patients with MS have been investigated in single-centre studies. The heterogeneity of used diagnostic criteria has influenced the variable findings of the studies dealing with the prevalence of PSS ranging from 0.2% in a Danish population to 3.9% in a population-based study in United States (reviewed in 6). Furthermore, the role that MS disease-modifying therapies (DMT) play in the occurrence of PSS has not yet been investigated. Over the last few years, the latter question has been raised in some reports that have investigated the appearance of PSS during the course of MS treated with IFN-beta, finding both a short time interval between MS onset and PSS occurrence accompanied by a poor response to treatment (7) and a long time interval and successful response to treatment (8). To address all these questions, we designed a large cross-sectional multicentre study with the aim of establishing the frequency of clinical features of PSS as well as PSS diagnosis, in relapsing–remitting (RR) and secondary progressive (SP) MS patients treated with immunomodulating drugs or naive to treatment. The possible association of these features with a number of clinical, cerebrospinal fluid (CSF) and conventional MRI parameters was also investigated.

Methods

Patients

The study cohort comprised 440 consecutive patients (306 women and 134 men) from five centres of northern, central and southern Italy with definite MS according to the McDonald criteria (9). The study ran from October 2006 to June 2007. Of 440 patients, 363 (75%) were RR and 77 (25%) SP. Two hundred and thirty patients (52%) were taking disease-modifying drugs ($DMDs^+$): 64 (28%) were on intramuscular IFN beta-1a once a week, 77 (33.5%) were on subcutaneous IFN beta-1a three times a week, 58 (25.2%) were on subcutaneous IFN beta-1b every other day and 31 (13.5%) on subcutaneous glatiramer acetate injections once daily. Two hundred and ten (48%) patients were naïve to treatment ($DMDs^-$).

Study design

This is a cross-sectional observational study based on a structured neurologist-administered questionnaire investigating the presence of clinical features of Sjogren's syndrome (SS) at the time of interview and at the time of MS onset. The questionnaire was structured to look for the presence of ocular and/or oral symptoms and ocular signs according to the items listed by the American-European Consensus Group (AECG) as classification criteria for SS (10). Patients complaining of dry eyes (xerophthalmia) or dry mouth (xerostomia) were asked to undergo laboratory (autoantibody screening) and instrumental tests (Schirmer's test) as well as histological tests (minor salivary gland biopsy) if the findings of the first two types of test were positive. Diagnosis of PSS was confirmed by rheumatologists according to the criteria proposed by the AECG. Patients taking immunosuppressive drugs or fulfilling the exclusion criteria for PSS proposed by the AECG (including HCV infection, AIDS, lymphoma, sarcoidosis and use of anticholinergic drugs) were not recruited for the study. At the time of administering the questionnaire, each patient was examined and neurological findings were recorded including the expanded disability status scale (EDSS). Neurological findings at the time of MS onset were obtained from clinical records. MRI scans performed within the 2 months prior to administration of the questionnaire were analysed in each centre by a neurologist expert in neuroimaging. When suggested by clinical symptoms, cognitive assessment was performed with the mini-mental state examination (MMSE) and mood function was assessed with the Hamilton rating scales for depression and anxiety or the Beck depression inventory. The number of T2-weighted and T1 gadolinium-enhancing positive lesions was assessed. All patients gave informed consent, and the study was approved by the Ethics Committee of the University of Siena (site of the coordinating centre) and the local ethics boards of the other investigating centres.

Statistical analysis

The statistical study was carried out univariately, testing the differences both between patients with (SS^+) and without (SS^-) clinical features of Sjogren's syndrome and among four groups formed by combining status with therapy, that is: SS^+DMDs^+, SS^+DMDs^-, SS^-DMDs^+ and SS^-DMDs^-. Because a preliminary investigation using the Kolmogorov–Smirnov test did not verify the normality of sample data, non-parametric tests were used for quantitative data comparison. In particular, we used the Mann–Whitney and the Kruskal–Wallis tests to compare two and four independent samples, respectively. Qualitative data were statistically analyzed by applying the Fisher exact test for 2×2 contingency tables or the Chi-square test for large contingency tables. Odds ratio and its 95% confidence interval (CI) were also estimated for 2×2 table analysis.

Multivariate logistic analysis was avoided because the low rate of SS^+ patients and the little occurrence of analysed risk factors in our sample do not allow to reach a satisfactorily statistical significance and power if factors are examined multivariately.

A significance level of 95% ($P \leq 0.05$) was considered for all statistical analyses. Statistical analyses were performed with the SPSS software package version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical and demographic characteristics

There were no significant differences with regard to the age of the patients taking or not disease-modifying drugs (39 ± 0.6 and 41 ± 0.8, respectively, $P = 0.085$) neither to the number of women and men (159:71 and 147:63, respectively, $P = 0.92$) nor to the number of relapsing–remitting and secondary progressive patients (192:38 and 171:39, respectively, $P = 0.61$). By contrast, the patients receiving immunomodulatory treatment had a significantly lower age at

onset (28 ± 0.6 and 31 ± 0.6, $P = 0.001$) and a significantly higher EDSS (2.7 ± 0.3 and 2 ± 0, $P = 0.038$) and disease duration (11 ± 0.5 and 10 ± 0.6, $P = 0.013$) than treatment-naïve patients.

Frequency of clinical features of SS

At the time of administering the questionnaire, 28 of 230 (12%) patients receiving treatment ($DMDs^+$) and 14 of 210 (6.6%) treatment-naïve patients ($DMDs^-$) showed clinical features of SS ($P = 0.053$). The frequency of patients with a SP course was 21% and 43% in SS feature-positive $DMDs^+$ and $DMDs^-$ patients, respectively, and 16% and 17% in SS feature-negative $DMDs^+$ and $DMDs^-$ patients, respectively ($\chi^2 = 6.98$, $P = 0.073$). There were no differences with regard to disease duration and EDSS at the disease onset between patients with and without clinical features of SS. Moreover, patients with clinical features of SS, both receiving treatment and treatment naïve, showed a significantly higher EDSS score at the time of questionnaire than those without ($P = 0.013$) (Table 1). There were no significant differences in terms of the presence or absence of SS features with regard to the type of immunomodulating drug ($\chi^2 = 4.04$, $P = 0.39$). Of the 42 SS feature-positive patients, 10 (24%) showed clinical features at the onset of MS. At the time of disease onset, a slightly higher frequency of visual disturbances was found in $DMDs^+$ patients with clinical features of SS, compared with the other groups ($P = 0.03$). At the time of questionnaire, either $DMDs^+$ or $DMDs^-$ patients with clinical features of SS had significantly higher frequency of sensory, visual and cerebral disturbances than those without SS features ($P = 0.004$, 0.03 and 0.0001, respectively). Of the seven patients with clinical features of SS and cerebral disturbances, five had depression and two presented mild or severe cognitive impairment. One of the five patients with depression was diagnosed with PSS (Table 2).

Laboratory and instrumental findings in patients with SS features

Thirty-nine of the 42 (93%) patients who were SS feature-positive at the time of the questionnaire agreed to undergo screening for anti-SSA and anti-SSB antibodies, and thirty-one of them (74%) agreed to undergo Schirmer's test. Anti-SSA and anti-SSB antibodies were detected in one of the 25 (4%) $DMDs^+$ patients compared with four of the 14 (28.6%) $DMDs^-$ patients ($P = 0.047$). Six of the 19 (31.6%) $DMDs^+$ patients who underwent Schirmer's test had a positive result when compared with 7 of 12 (58%) $DMDs^-$ patients ($P = 0.26$). Of the patients with auto-antibody screening and a positive Schirmer's test, three agreed to undergo minor salivary gland biopsy and two of these showed a positive pattern according to the AECG criteria. Based on the AECG criteria, four MS subjects were diagnosed as having PSS: two of these were $DMDs^+$ and two $DMDs^-$.

Cerebrospinal fluid and MRI parameters

At the time of MS diagnosis, 261 of the 440 (59.3%) patients underwent CSF analysis. There were no differences between $DMDs^+$ and $DMDs^-$ patients with or without clinical features of SS with regard to IgG and IgG index, but there were higher number of cells in $DMDs^+$ patients without clinical features of SS ($P = 0.02$) and a slightly higher protein content in $DMDs^-$ patients with clinical features of SS ($P = 0.022$) (Table 3). Brain MRI scans were available for 365 of the 440 (83%) patients at the time of the questionnaire. Of the patients for whom MRI scans were available, 35 patients presented clinical features of SS. Of these, none of the 22 (0%) $DMDs^+$ and 2 of 13 (15.4%) $DMDs^-$ showed gadolinium-enhancing lesions compared with 64 of the 330 (19.4%) patients without clinical features of SS ($\chi^2 = 10$; $P = 0.018$). A higher average number of supratentorial gadolinium-enhancing lesions was

Table 1 Association of multiple sclerosis (MS) clinical parameters with clinical features of SS

	SS^+ $DMDs^+$ ($n = 28$)	SS^+DMDs^- ($n = 14$)	SS^- $DMDs^+$ ($n = 202$)	SS^- $DMDs^-$ ($n = 196$)	P
Disease duration (years)	12.6 ± 1.7	8.5 ± 1.9	11.3 ± 0.5	10.3 ± 0.6	0.062
RR:SP (n) (%)	22:6 (79:21)	8:6 (57:43)	170:32 (84:16)	163:33 (83:17)	0.073
EDSS (onset)	1.9 ± 0.3	1.7 ± 0.3	1.6 ± 0.1	1.4 ± 0.1	0.13
EDSS (questionnaire)	2.5 ± 0.4	3.3 ± 0.7	2.2 ± 0.1	1.9 ± 0.2	0.013

SS, Sjogren's syndrome; n, number of subjects; RR:SP, relapsing–remitting:secondary progressive patients; EDSS, Expanded disability status scale; SS^+ $DMDs^+$, patients on disease-modifying drugs with clinical features of SS; SS^+ $DMDs^-$, patients naïve to treatment with clinical features of SS; SS^- $DMDs^+$, patients on disease-modifying drugs without clinical features of SS; SS^- $DMDs^-$, patients naïve to treatment without clinical features of SS.

Multiple comparisons were made with Kruskal–Wallis test. Frequency analysis was performed with Chi-square test for large contingency tables. The results are expressed as mean ± SEM.

Table 2 Association of clinical neurological signs at the multiple sclerosis (MS) onset and at the time of the questionnaire with clinical features of SS

	SS^+ $DMDs^+$ (%)	SS^+ $DMDs^-$ (%)	SS^- $DMDs^+$ (%)	SS^- $DMDs^-$ (%)	*P*
MS onset					
Brainstem	8 (29)	3 (21)	37 (18)	26 (13)	0.11
Cerebellar	3 (11)	1 (7)	16 (8)	20 (10)	0.85
Pyramidal	13 (46)	4 (29)	65 (32)	54 (28)	0.22
Sensory	9 (32)	2 (14)	62 (31)	54 (28)	0.55
Bladder	0 (0)	1 (7)	9 (4)	4 (2)	0.31
Visual	3 (11)	7 (50)	59 (29)	65 (33)	0.03
Cerebral	0 (0)	0 (0)	0 (0)	3 (1.5)	0.29
Time of the questionnaire					
Brainstem	5 (18)	3 (21)	21 (10)	17 (9)	0.25
Cerebellar	7 (25)	3 (21)	38 (19)	38 (19)	0.89
Pyramidal	21 (75)	10 (71)	137 (68)	113 (58)	0.09
Sensory	8 (29)	5 (36)	38 (19)	39 (20)	0.004
Bladder	7 (25)	5 (36)	42 (21)	32 (16)	0.22
Visual	5 (18)	4 (29)	15 (7)	20 (10)	0.03
Cerebral	4 (14)	3 (21)	3 (1.5)	5 (2.5)	0.0001

SS, Sjogren's syndrome. SS^+ $DMDs^+$, patients on disease-modifying drugs with clinical features of SS; SS^+ $DMDs^-$, patients naïve to treatment with clinical features of SS; SS^- $DMDs^+$, patients on disease-modifying drugs without clinical features of SS; SS^- $DMDs^-$, patients naïve to treatment without clinical features of SS.

For each sign, frequency analysis was performed with Chi-square test for large contingency tables.

detected in patients without clinical features of SS ($P = 0.007$). There were no significant differences between the groups of patients in terms of T2-weighted lesions except for a higher average number of T2-weighted infratentorial lesions in $DMDs^+$ patients without clinical features of SS ($P = 0.003$) (Table 3).

Analysis of parameters associated with clinical features of SS

We found that at the time of the questionnaire, visual signs ($P = 0.025$), disability ($P = 0.018$) and cerebral disturbances ($P = 0.001$) were significantly associated with the presence of clinical features of SS (Table 4).

Discussion

This study demonstrates that the clinical features of sicca complex (xerostomia and xerophthalmia), which are classical symptoms of SS, may occur during the course of MS both in subjects receiving immunomodulatory treatment and in treatment-naïve subjects and have a trend to arise, although not exclusively, during a progressive course. In this large multicentre cohort, four PSS were diagnosed giving a PSS prevalence of 0.91%. Other studies based on limited size MS cohorts from single centres have also administered questionnaires to investigate the prevalence of PSS among patients with MS and found a prevalence ranging from 0 to 3.3% (1–3). However, all these studies employed heterogeneous criteria to establish the diagnosis of PSS. In our study, we used a questionnaire structured with the items listed by the AECG, and diagnosis of PSS was performed according to the AECG criteria that show high sensitivity (96.1%) and specificity (94.2%) (10). Furthermore, none of the previous studies have investigated the role played by immunomodulatory therapies. In the last few years, a number of single case reports have shown treatment with IFN-beta to be associated with the occurrence of PSS during the course of MS in non-responder patients as well as in good responders at time intervals from the onset of MS ranging from a few months to many years (7, 8).

We found a slightly higher prevalence of sicca complex symptoms in patients with MS taking immunomodulatory drugs than in those without therapy, but this finding did not reach significance and therefore does not support a possible pathogenic role of DMDs in the occurrence of sicca complex symptoms. In the patients with SS features, we found a low prevalence of anti-SSA and anti-SSB antibodies, confirming the low association of these autoantibodies with the clinical features of SS (5).

Xerostomia and xerophthalmia in SS are thought to be the result of extending lymphocytic infiltration of the salivary and lacrimal gland acinar epithelium leading to glandular dysfunction (11). It is likely that, in MS, a different mechanism accounts for the appearance of oral or ocular dryness. The possible influence of any drug on the occurrence of xerostomia and xerophthalmia in our patients may be ruled out as patients taking anticholinergic drugs (known to reduce lacrimation and salivation), at the time of the questionnaire, were excluded from the study. In a recent prospective study assessing the occurrence of autonomic dysfunction in MS, vasosecretory motor symptoms including dryness of mouth or eyes were detected more frequently than other autonomic symptoms such as gastroenteric symptoms as well as bladder and sexual dysfunctions (12). This finding suggests that oral and ocular dryness in MS may be associated with autonomic dysfunctions. In MS, autonomic dysfunction is heterogeneous and may involve both parasympathetic and sympathetic system (13). Although we did not search for autonomic dysfunctions in our cohort, it cannot therefore be ruled out that the occurrence of sicca complex symptoms depends on alterations of the autonomic nervous system. In our study, the significant association of clinical features of SS

Table 3 Association of cerebrospinal fluid and magnetic resonance imaging (MRI) findings with clinical features of SS

	SS^+ $DMDs^+$ (n = 15)	SS^+ $DMDs^-$ (n = 10)	SS^- $DMDs^+$ (n = 117)	SS^- $DMDs^-$ (n = 119)	P
Cerebrospinal fluid (n = 261)					
Cells (n/μl)	3.9 ± 1.6	2.5 ± 0.85	7.6 ± 3	2.3 ± 0.4	0.02
Protein (mg/dl)	36.6 ± 4	49 ± 4	37.7 ± 2	40 ± 1.6	0.022
IgG (mg/dl)	5.5 ± 0.99	5.9 ± 1	5.4 ± 0.5	4.8 ± 0.38	0.46
IgG index	1 ± 0.17	0.93 ± 0.3	0.93 ± 0.05	0.88 ± 0.08	0.25
OB^+ (n)	12 (80%)	9 (90%)	105 (89%)	101 (85%)	0.57
	SS^+ $DMDs^+$ (n = 22)	SS^+ $DMDs^-$ (n = 13)	SS^- $DMDs^+$ (n = 168)	SS^- $DMDs^-$ (n = 162)	P
Brain MRI (n = 365)					
T2- tot. (n)	9.3 ± 0.8	11.6 ± 3.6	11.0.±0.65	10.9 ± 0.95	0.94
T2- sup. (n)	7.1 ± 0.6	9.7 ± 2.8	8.4 ± 0.7	9.5 ± 0.99	0.75
T2- inf. (n)	2.2 ± 0.5	1.9 ± 0.9	2.6 ± 0.3	1.4 ± 0.2	0.003
GAD^+ pts (n)	0 (0%)	2 (15.4%)	25 (17.5%)	39 (31.7%)	0.018
GAD^+ sup (n)	0 ± 0	0.2 ± 0.2	0.2 ± 0.06	0.4 ± 0.09	0.007
GAD^+ inf (n)	0 ± 0	0.08 ± 0.08	0.05 ± 0.02	0.08 ± 0.03	0.45

SS, Sjogren's syndrome; SS^+ $DMDs^+$, patients on disease-modifying drugs with clinical features of SS; SS^+ $DMDs^-$, patients naïve to treatment with clinical features of SS; SS^- $DMDs^+$, patients on disease-modifying drugs without clinical features of SS; SS^- $DMDs^-$, patients naïve to treatment without clinical features of SS. n, number; OB^+, patients with oligoclonal bands; GAD^+ pts, patients with gadolinium-enhancing lesions; T2-total, total T2-weighted lesions; T2- sup, supratentorial T2-weighted lesions; T2-inf, infratentorial T2-weighted lesions; GAD^+ sup, supratentorial gadolinium-enhancing lesions; GAD^+ inf, infratentorial gadolinium-enhancing lesions.

Multiple comparisons were made with Kruskal–Wallis test. For OB^+ and GAD^+, frequency analysis was performed with Chi-square test for large contingency tables. The results are expressed as mean ± SEM.

Table 4 Analysis of variables associated with clinical features of SS

Variable	P	OR	95% CI
Gender	0.601		
Therapy	0.053		
Disease course (RR,SP)	0.055		
Age	0.585		
Age at onset	0.983		
Disease duration	0.831		
EDSS at the onset	0.089		
EDSS at the questionnaire	0.018		
Visual signs at the onset	0.599		
Visual signs at the questionnaire	0.025	2.8	1.3–6.4
Sensory signs at the onset	0.723		
Sensory signs at the questionnaire	0.067		
Cerebral disturbances at the onset	1.000		
Cerebral disturbances at the questionnaire	0.001	5.9	2.2–15.8
GAD^+	0.061		

RR, relapsing–remitting; SP, secondary progressive; GAD^+, patients with gadolinium-enhancing lesions; OR, odds ratio; CI, confidence interval.

Statistical differences of quantitative variables are evaluated with the Mann–Whitney test. 2 × 2 contingency tables of binary variables are analysed with the Fisher exact test by evaluating also its OR and the related 95% CI when statistically significant ($P < 0.05$).

with a higher EDSS score than in other patients is consistent with the finding of a significant relationship of parasympathetic dysfunction with the progression of disability in MS (14). This data is further supported by the correlation between autonomic alterations and cervical spinal cord atrophy, suggesting that some autonomic dysfunctions in MS may be the result of axonal loss involving also the autonomic nervous system tracts (15). Our study, which, except for a report on the prevalence of SS in patients with primary progressive MS (16), is the first one to investigate the role of MRI parameters in identifying the occurrence of clinical features of SS in relapsing and secondary progressive MS, did not search for brain or spinal cord atrophy in our patients. However, the low prevalence of gadolinium-enhancing lesions in patients with sicca symptoms supports the relationship of these symptoms with a low inflammatory disease activity as also suggested by the statistical trend towards the association between oral and ocular dryness in this cohort with a secondary progressive course known to be associated mainly with axonal loss and seldom with inflammatory pattern.

The high prevalence of cerebral disturbances in patients with sicca symptoms found in our cohort needs further investigation and requires a cautious interpretation because of the small size of the sample (seven patients) and to the possibility that we have underestimated more subtle cognitive changes detectable with appropriate neuropsychological batteries in both patients with and without sicca complex symptoms (17, 18).

In conclusion, our study confirms a low prevalence of SS in patients with MS when stringent diagnostic criteria are used and suggests that screening for the clinical features of SS should be performed in patients with MS receiving treatment with immunomodulatory drugs and in those without therapy. However, the diagnosis of PSS during

the course of MS requires a selective treatment that depends on the clinical picture of PSS, regarding the use of muscarinic agonists for ocular sicca symptoms as well as immunosuppressive or immunomodulatory drugs such as the questionable anti-TNF-alpha agents (inadvisable for MS) or the more promising B-cell-targeted therapies with monoclonal antibodies (rituximab, under investigation in MS, and epratuzumab) for severe extraglandular progressive symptoms (19). Further large prospective studies are warranted to establish whether the occurrence of sicca complex symptoms is associated with other autonomic dysfunctions in patients with MS.

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