Fibromyalgia prevalence and associated factors in primary Sjögren's syndrome patients in a large cohort from the Spanish Society of Rheumatology registry (SJOGRENSER)

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ABSTRACT

Objective. *To assess fibromyalgia (FM) prevalence in a large cohort of primary Sjögren's syndrome patients (pSS) from a National Database.*

Methods. *Data included in the national retrospective register of pSS patients of the Spanish Society of Rheumatology (SJOGRENSER) were analysed.*

Results. *437 pSS patients were included and a 14.6% of FM prevalence was found. FM-pSS patients significantly showed more constitutional, fatigue and arthralgia symptoms, splenomegaly, genital, skin and ear involvement and dyslipidaemia ($p<0.05$), as well as higher ESSPRI and SSDAI scores ($p<0.01$). Several symptomatic treatments were more frequently used in FM-pSS patients. No differences were observed in laboratory markers, imaging techniques or histologic inflammatory findings. Patients with FM showed statistically more fatigue than pSS without FM. In the multivariate logistic regression analysis several features were associated to pSS-FM patients.*

Conclusion. *We show data on a reliable prevalence of FM in pSS patients and its multiple associated factors along with the presence of higher disease activity scores than patients who did not show FM. The presence of fatigue, arthralgia, constitutional symptoms and dyslipidaemia were more likely to coexist in pSS-FM patients.*

Introduction

Besides the more frequent and main oral and ocular dryness symptoms that constitutes the primary Sjögren's syndrome (pSS), there is the knowledge that chronic widespread myalgia, also known as fibromyalgia (FM), is a frequent complaint in patients with pSS. The 1990 American College of Rheumatology (ACR) classification criteria for FM require widespread pain in combination with tenderness at 11 or more of the 18 specific tender point sites (1). Several investigations have established that FM prevalence in pSS ranges from 6.9 to 55% (2-7). This wide range probably steams on the heterogeneous geographic populations, diagnostic criteria and study designs studied. It is noteworthy that the largest series among them included only 92 patients. Some authors have pointed out the different expression pattern in peripheral blood cytokine expression profile in pSS patients with FM (compared to other systemic autoimmune diseases) supporting an immune-pathogenic role in this impairing manifestation (8). Besides, it has been posted that myositis histologic signs are found in up to 72% of pSS with FM (9). On the other hand, other authors have related the presence of FM in patients suffering from specific oral symptoms, including oral dryness or sicca symptoms, in general population (10). Usually, those pSS patients who suffer from FM also complain of fatigue. Fatigue is one of the most frequent, disabling and intriguing symptoms that pSS patients show throughout the course of the disease. However, its prevalence is known higher than FM symptoms and not always associated to FM (11). Because of all the above mentioned, there is a need to study the prevalence of FM symptoms in pSS patients and associated factors in a larger group of patients.

We aimed to establish the prevalence of FM and its associated factors in pSS. We also aimed to assess whether the presence of fatigue and specific pSS serological biomarkers are associated

to FM in a large community of pSS patients in Spain.

Patients and methods

Study design and research study network

Selected data for the purposes of this study were obtained from the SJOGRENSER-T Registry and were analysed accordingly (see *Variables* paragraph). The objectives and methodology of the SJOGRENSER-T Registry have been already published (12). A scientific committee approved the study project.

Study population

Out of 437 pSS-diagnosed patients enrolled in the SJOGRENSER-T Registry, all of those patients who fulfilled European-American Consensus Group (EACC) (13) classification criteria were included. This registry was performed between 2013 and 2014 over a 10-month period of time. An online monitored control was used to clarify all inconsistencies, missing values, and discrepancies.

Variables

Sociodemographic factors: age, ethnicity, sex, age at onset, delay of diagnosis, and disease duration.

Clinical variables included: ocular, oral, genital, skin and ear dryness; nasopharyngeal, sinuses, pharyngo-laryngeal and constitutional symptoms; lymphadenopathy, salivary glandular inflammation, splenomegaly, Raynaud's phenomenon; haematological, renal, central and peripheral nervous systems, gastrointestinal, hepatic, pancreatic, cardiac and respiratory involvement; FM, arthralgia, arthritis; fatigue.

FM was defined according to ACR 1990 classification criteria (1) if present at some stage over the course of pSS.

Data regarding co-morbidities included: hypothyroidism, osteoporosis, osteoporotic fracture, dyslipidaemia, arterial hypertension, cases of severe infections that lead to hospitalisation and number of hospitalisations due to pSS worsening.

Laboratory markers: antinuclear antibodies (ANA), anti-Ro/SS-A (RO) and anti-La/SS-B (LA) antibodies,

Table I. Clinical and serological features in pSS patients with and without FM.

Variable	pSS without FM n (%)	pSS with FM n (%)	*p*-value
Sociodemographics			
Age (mean (SD))	58.83 (13.35)	59.19 (9.55)	0.831
Gender (Female/Male)	352 (94.37) / 21 (5.63)	64 (100)/ / 0 (0)	0.052
Ethnicity:			
- Caucasian	346 (92.76)	62 (96.88)	
- African	1 (0.27)	0 (0)	
- Asian	0 (0)	1 (1.56)	0.168
- Hispanic	25 (6.7)	1 (1.56)	
- Gipsy	1 (0.27)	0 (0)	
Clinical and Serological involvement over time			
Ocular symptoms	366 (98.12)	64 (100.00)	0.269
Oral symptoms	365 (97.86)	64 (100.00)	0.237
Genital involvement	166 (44.50)	48 (75.00)	<0.001
Ear involvement	168 (45.04)	39 (60.94)	0.019
Pharyngeal-Amygdala symptoms	56 (33.33)	11 (28.21)	0.537
Sinuses symptoms	97 (57.74)	23 (58.97)	0.888
Pharyngeal-Laryngeal involvement	146 (39.46)	33 (51.56)	0.069
Constitutional symptoms	59 (15.82)	19 (29.69)	0.007
Glandular inflammation	118 (31.64)	24 (37.50)	0.355
Lymphadenopathy	64 (17.16)	5 (7.81)	0.058
Splenomegaly	2 (0.54)	2 (3.13)	0.045
Lymphoma	7 (1.88)	0 (0)	0.269
Raynaud's phenomenon	74 (19.84)	18 (28.13)	0.133
Abnormal Salivary Gland Scintigraphy	186 (49.87)	35 (54.69)	0.170
Myopathy	9 (2.41)	1 (1.56)	0.674
Haematological involvement	214 (57.37)	30 (46.88)	0.118
Arthralgia	294 (78.82)	59 (92.19)	0.012
Arthritis	135 (36.19)	16 (25.00)	0.082
Skin dryness	262 (70.43)	54 (84.38)	0.021
Renal involvement	36 (9.68)	3 (4.69)	0.196
Respiratory involvement	38 (10.22)	5 (7.81)	0.552
Cardiac involvement	11 (2.96)	2 (3.13)	0.942
Central Nervous System involvement	30 (8.06)	4 (6.25)	0.617
Minor salivary gland biopsy			
Normal	15 (78.95)	4 (21.05)	0.182
Mild infiltrate	16 (72.73)	6 (27.27)	
Moderate infiltrate	14 (73.68)	5 (26.32)	
1 focus	30 (81.08)	7 (18.92)	
≥ 2 focus	85 (88.54)	11 (11.46)	
Unknown	213 (87.3)	31 (12.7)	
Peripheral Nervous System involvement	33 (8.87)	6 (9.38)	0.896
Gastrointestinal involvement	47 (12.60)	12 (18.75)	0.184
Liver involvement	26 (6.97)	7 (10.94)	0.267
Pancreatic involvement	5 (1.34)	2 (3.13)	0.293
Thyroidal involvement			
None	307 (82.31)	51 (79.69)	0.611
Subclinical hypothyroidism	19 (5.09)	4 (6.25)	
Autoimmune hypothyroidism	36 (9.65)	5 (7.81)	
Autoimmune hyperthyroidism	1 (0.27)	1 (1.56)	
Autoimmune hypothyroidism (anti-TPO -)	9 (2.41)	3 (4.69)	
Low C3 complement	59 (15.82)	6 (9.38)	0.078
Low C4 complement	52 (13.94)	10 (15.63)	0.129
Hyper-gammaglobulintumour	200 (53.62)	30 (46.88)	0.601
Raised β2-microglobulin	83 (22.37)	14 (22.58)	0.990
Anti-nuclear Antibodies positivity	363 (97.32)	61 (95.31)	0.383
Highest Anti-nuclear Antibodies titres over time			
Negative	22 (6.06)	3 (5.00)	0.357
1/160	36 (9.92)	4 (6.67)	
1/320	86 (23.69)	14 (23.33)	
1/640	88 (24.24)	22 (36.67)	
1/1280	65 (17.91)	12 (20.00)	

Variable	pSS without FM n (%)	pSS with FM n (%)	*p*-value
Titre increase	51 (14.05)	5 (8.33)	
Unknown	15 (4.13)	0 (0.00)	
Rheumatoid Factor positivity	119 (31.90)	24 (37.50)	0.315
Anti-Ro Antibody	331 (94.03%)	58 (90.63%)	0.309
Anti-La Antibody	237 (67.33%)	42 (65.63%)	0.79
Raised Ig G	186 (49.87)	24 (37.50)	0.077
Raised Ig M	10 (2.68)	3 (4.69)	0.646
Raised Ig M	77 (20.64)	11 (17.19)	0.511
Comorbidities			
Dyslipidaemia	113 (30.29)	32 (50.00)	0.002
Osteoporosis	65 (17.43)	15 (23.44)	0.251
Osteoporotic Fracture	31 (8.40)	6 (9.68)	0.740
Hospitalisation due to pSS activity	66 (17.69)	9 (14.06)	0.477
Severe Infection leading to hospitalisation	39 (10.46)	5 (7.81)	0.740
Arterial Hypertension	90 (24.13)	22 (34.38)	0.083
Fatigue symptoms			
pSS-related Fatigue	220 (58.98)	56 (87.50)	<0.001
Fatigue diagnosed before pSS onset	86 (39.09)	26 (47.27)	0.866
Fatigue at pSS diagnosis	40 (18.18)	9 (16.36)	
Fatigue within 2 years after pSS diagnosis	40 (18.18)	10 (18.18)	
Fatigue within 2-5 years after pSS diagnosis	34 (15.45)	6 (10.91)	
Fatigue within 5-10 years after pSS diagnosis	13 (5.91)	2 (3.64)	
Fatigue > 10 years after pSS diagnosis	7 (3.18)	2 (3.64)	
Fatigue at last visit	52 (13.94)	35 (54.69)	<0.001
New onset Fatigue or worsening	31 (8.31)	17 (26.56)	<0.001
Most relevant treatments (only those with *p*-value <0.05)			
Non-Steroidal Anti-Inflammatory drugs			
Never	68 (18.58)	3 (4.69)	0-008
Current	142 (38.80)	35 (54.69)	
In the past	156 (42.62)	26 (40.63)	
Current use of specific vaginal soap	37 (10.45)	15 (23.44)	0.013
Current use of specific hydrating body cream	142 (39.66)	37 (57.81)	0.019
Vaginal Lubricants	73 (20.68)	21 (32.81)	0.003
Hands specific soap	22 (6.20)	13 (20.31)	0.001
Activity pSS specific Indexes**			
Cutaneous-mucous Dryness Scale^ (VAS 0-10 mm)	6 [4-8]	7 [6-9]	<0.001
Fatigue^ (VAS 0-10 mm)	5 [4-8]	8 [5-9]	<0.001
Widespread Pain^ (VAS 0-10 mm)	5 [2-7]	8 [6-9.5]	<0.001
ESSDAI	3 [1-9]	2 [1-5]	0.250
SSDAI	1 [0-2]	2 [1-3.5]	<0.001
SSDDI	2 [1-3]	2 [1-3]	0.858

**results shown in Median [range]; ^ESSPRI items.
SD: Standard deviation; pSS: primary Sjögren Syndrome; FM: fibromyalgia; Ig: immunoglobuline: mm: millimetres; ESSPRI: Eular Sjögren's Syndrome Patient Reported Index; SSDAI: Sjögren's Syndrome Disease Activity Index; SSDDI: Sjögren's Syndrome Disease Damage Index; VAS: Visual Analogue Scale.

rheumatoid factor (RF), peripheral immunoglobulin (IgG and IgM), presence of haemolytic anaemia, leucopenia, lymphopenia, thrombocytopenia, hypergammaglobulinaemia, β2-microglobulin and hypocomplementaemia (14).

Histologic findings in minor salivary gland were recorded, as presence of none, 1 or ≥2 limphoplasmacytic foci, based on Chisholm classification (15). Evidence of abnormal salivary scintigraphy (Tc^{99}) was recorded.

We also collected data from several pSS related symptoms and activity indexes: the Eular Sjögren's Syndrome Patient Reported Index (ESSPRI) (16); the EULAR Sjögren's syndrome disease activity index (ESSDAI) (17); Sjögren's syndrome disease activity index (SSDAI) (18), Sjögren's syndrome disease damage index (SSDDI) (19). For the ESSPRI items completion patients rated pain, fatigue and disease activity using a 10-cm visual analogue scale.

We recorded all data treatment, including symptomatic measures (such as gums, humidificants, lubricants or artificial tears, among others), and specific treatments. Among the latter we included the following: previous use of oral steroids (mean daily intake (<10 mg, 11–29 mg, >29 mg), immunosuppressant drugs, immunoglobulin, organ-specific related drugs, biological therapies, local surgery and dialysis.

All variables-related information was classified as 'present' if they occurred at any time since pSS onset (12). A specific guideline of codes and definitions for all SJOGRENSER-T investigators was created to standardise and clarify data collection.

Statistical analyses

Means and standard deviations or medians and interquartile percentiles for numeric variables based on normal distribution, as well as absolute and relative frequencies for categorical variables, were calculated. Global and segmented population-based analyses on the presence of fibromyalgia (FM) and pSS disease duration were carried out. The relation of each independent variable with the dependent variable (FM) was assessed by applying statistical tests: the Student's *t*-test for numerical variables and the Chi-squared test for comparing categorical variables among groups. Finally, in order to those factors associated with the presence of FM, an assessment calculating crude odds ratios and adjusted odds ratio with confounding factors (OR) through logistic regression was made. The multivariate model included as independent variables those that had a statistically significant result in the bivariate analysis and those deemed clinically relevant or possible confounders; however, if the included variables showed any significant correlation, they were excluded from the model. Statistically significance was assumed as $p<0.05$. All analyses were performed using

SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 437 patients were included whose 64 showed FM (14.6%). No differences regarding the following baseline characteristics were seen: median age was 58.55 years (49.17–68.39), age at the beginning of symptoms 47.53 years (35.45–56.68), age at diagnosis 50.83 years (41.10–59.89), mostly female (95.2%) and Caucasian ethnicity (93.36%).

In Table I we show all variables we assessed to demonstrate association to the presence of FM ($p<0.05$). In summary, pSS with FM showed more constitutional, fatigue and arthralgia symptoms, splenomegaly, genital, skin and ear involvement and dyslipidaemia. As shown in Table I, several treatments related to the latter manifestations were also more used in these patients. pSS with FM also showed higher scores in SSDAI index ($p<0.001$). No differences were observed in laboratory markers, scintigraphy or histologic abnormalities. The prevalence of fatigue in pSS with or without FM over time is also shown in Table I.

In the Supplementary material we show all pSS associated treatments analyses based on the presence of FM (p=NS). In the same section it is shown the comparison between fatigue and non-fatigue pSS patients in terms of autoantibodies presence.

From all statistical significant variables, we performed a univariate (Table II) and multivariate logistic regression (Table III) analyses. A higher OR for the presence of FM was found in pSS who showed fatigue, arthralgia, constitutional symptoms and dyslipidaemia.

Table II. Univariate analysis: assessment of the association of FM to pSS-related variables detected in the descriptive model.

Description	Odds ratio	Confidence interval 95%	*p*-value
Genital involvement	3.74	(2.05; 6.83)	<0.001
Ear involvement	1.90	(1.11; 3.27)	0.02
Constitutional symptoms	2.25	(1.23; 4.11)	0.009
Splenomegaly	5.98	(0.83; 43.27)	0.076
Arthralgia	3.17	(1.23; 8.17)	0.017
Skin dryness	2.27	(1.11; 4.61)	0.024
Dyslipidaemia	2.30	(1.34; 3.94)	0.002
Non-Steroidal Anti-Inflammatory drugs			
- Current	5.59	(1.66; 18.81)	0.005
- In the past	3.78	(1.11; 12.91)	0.034
Current Hands specific Soap	3.84	(1.82; 8.09)	<0.001
Current specific vaginal soap	2.58	(1.31; 5.05)	0.006
Current Vaginal Lubricants	2.19	(1.20; 4.00)	0.011
pSS-related Fatigue over time	4.87	(2.26; 10.50)	<0.001
Fatigue at last visit	7.45	(4.20; 13.21)	<0.001
New onset Fatigue or worsening	3.99	(2.05; 7.76)	<0.001

pSS: Primary Sjögren syndrome; FM: fibromyalgia.

Table III. Multivariate logistic regression logistic model.

Variable	Odds ratio	Confidence interval	*p*-value
Fatigue at last visit	7.52	(4.08; 13.84)	0.000
Arthralgia	3.18	(1.14; 8.87)	0.027
Constitutional symptoms	2.86	(1.38; 5.94)	0.005
Dyslipidaemia	1.95	(1.04; 3.65)	0.038

Discussion

In this study we found a 14.6% of prevalence of FM in mostly Caucasian pSS patients, which is in according of more recent published data than older clinical studies. This prevalence probably differs substantially from previous observations (6.9–57%) (2-7) and would seem low. However, we consider this prevalence more reliable than others shown by other authors since our work included the highest number of pSS for this purpose compared to theirs. In a very recent similar task force, the prevalence of FM in mostly Caucasian Systemic Lupus Erythematosus patients was found to be 6.2% (20), which enhances that FM would be a more important concern in pSS than in other connective tissue diseases.

We assessed all clinical, laboratory and therapeutic data in order to detect associated factors to the presence of FM in pSS. Depression has been related to the presence of FM in pSS (4) and in other connective tissue diseases (20). Oral dryness (and other oral symptoms such as glossodynia, dysphagia and dysgeusia) (10) had been related to the presence of widespread pain in primary FM patients and in patients with FM and other Rheumatologic conditions (7). We could not confirm this observation in our FM-pSS patients. Besides, this is the second published work assessing the relationship between the presence of FM and the severity of the histologic changes in labial biopsy in pSS (21). Again, we did not find any association between the presence of FM with either 0, 1 or >1 foci infiltrate in labial biopsy. Therefore, it seems that severity of inflammatory oral involvement has no relationship to FM in pSS.

Among all clinical symptoms associated to pSS, genital and ear involvement, splenomegaly, constitutional symptoms, skin dryness and arthralgia were associated to the presence of FM in pSS, which has not been previously described.

None of all laboratory markers were found to be associated to the presence of FM. Neither was found a relationship between FM and the presence of specific autoantibodies (Ro and La) and ANA positivity.

When comparing FM and non-FM pSS patients, we found that SSDAI activity index was higher in FM-pSS patients. The latter has also been found in other inflammatory or systemic diseases, such as rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis (7). This may rely on the fact that pSS patients who also showed FM had, actually, higher degree of pSS

activity. Moreover, this observation would due to the presence of fatigue by itself, which has been frequently associated to FM in pSS patients. The latter would be criticised by the intrinsic nature of this index, which include subjective patients' opinion such as Fatigue. We consider looking for other strategies to measure disease activity in pSS patients who also show FM, as the presence of FM by itself would be confusing for the assessment of clinical activity in pSS, as also have been demonstrated in other diseases (20).

It has been stated that fatigue symptoms may appear in 68–74% of pSS patients and its direct relationship to pSS might be difficult to both define and measure it (22). It has been also observed that the presence of fatigue in pSS patients is not related to the presence of overall disease activity, specific auto-antibodies or laboratory markers, except for the co-existence of a lymphopenia (23-25). The co-existence of fatigue and FM is very frequent, although not all patients with fatigue also show FM. We found that FM-pSS showed more frequently fatigue (87%) than those who did not show FM (58%), which is lower than other authors have observed (90.9 to 100%) (7, 21). An overall 50.3% showed fatigue alone, which is in accordance to other previous observations (36–100%) (7). Whether the fatigue that appears in FM-pSS patients is related to the presence of FM by itself or the pSS is yet to be clarified (11, 22). One limitation of our study is that we could not assess the influence of mood disorders in these observations, which have been related to both the presence of fatigue and FM in pSS patients. Besides, we did not specifically assess the levels of several cytokines that have been related to the presence of fatigue (22). However, we did assess the presence of Fatigue and its relationship with specific autoantibodies and histological findings (Chisholm and Mason scale), and we only found that patients with Fatigue also showed low titter of ANA compared to non-Fatigue patients (Supplementary material).

The presence of FM in pSS patients has been associated to a milder lymphocytic infiltrate in their minor salivary glands, to a lesser need for systemic medication and to the presence of scant extra glandular manifestations (21). Giles *et al*. observed a lower prevalence of ANA, anti-Ro and anti-La antibodies in FM-pSS patients compared to those without FM, although these differences were non-significant statistically (11). However, other authors did not find specific associated both clinical and laboratory pSS-related factors in an observational study, except for the presence of sleep disturbances, which was also associated to the presence of fatigue (6, 26). In an observational study, the presence of FM was associated to psychopathological changes (4), particularly depression. Moreover, an Italian work found the presence of purpura, hypergammaglobulinaemia, rheumatoid factor, and a focus score ≥1 on lip biopsy in pSS patients were significantly associated to the absence of FM (21). We did not find any of these laboratory associations in our work. However, we found several new described factors related to the presence of FM in pSS: constitutional, fatigue and arthralgia symptoms, splenomegaly, genital, skin and ear involvement and dyslipidaemia. Among them, in the multivariate logistic regression model fatigue, arthralgia, constitutional symptoms and dyslipidaemia were associated to FM. Based in our results, this specific 'subgroup' of pSS patients (those who also show splenomegaly, constitutional symptoms) seem to have higher probabilities of developing FM. How dyslipidaemia would relate to this condition should be further investigated, although some authors have raised the possibility that primary FM patients might show abnormal cholesterol metabolism that lead to higher free cholesterol levels (27). Regarding this latter, and possibly other somatic features (genital, skin and ear involvement) we found more associated to FM in pSS, we could hypothesise that they would be related to the presence of FM by itself, as primary FM symptoms usually trend to predominate in the clinical course of FM patients (28). Disease activity do not seem to be specifically related to the presence of FM, as previously posted (7). However, we found that pSS with FM showed higher scores in activity SSDAI index. The latter would be explained by the presence of several items concerning associated clinical factors to FM in pSS, described above, within this index (*fatigue* may score up to 2 points in Constitutional Symptoms of SSDAI index). The presence of higher activity measured by SSDAI in pSS-FM patients would be related to the fact that these patients also use more non-steroidal anti-inflammatory drugs, specific vaginal soap and hydrating body cream, vaginal lubricants and hand specific soap. FM in pSS has been related to a milder immunological and inflammatory disease phenotype with less consumption of systemic medications (21). However, we show that pSS patients with FM also showed impairing pSS typical and atypical symptoms and comorbidities, which would not be exactly related to a 'mild' disease. Whether the pSS involvement described that are associated to FM are linked to stressful life events, mood disorders (one limitation of our study is that Depression was not assessed), specific psychopathological clusters (29), or more severe immunological and inflammatory glandular changes are yet to be confirmed. Besides, another limitation for the correct interpretation of our results on ESSPRI data was that we did not collect data on physical activity since it may improve ESSPRI scores in pSS patients (30). The latter, if recorded, would facilitate to understand differences on ESSPRI between both groups, but based in our results, particularly in non-FM pSS patients as they scored statistically better in ESSPRI items. Similarly, we are able to add more evidence with these findings to the very similar previous observations observed by Choi *et al*. (31).

As limitations of our study, we considered the retrospective collection of clinical and laboratory characteristics of patients at the time of inclusion in the study. These type of studies may have some problems: lack of control over the quality of information, measurement errors that can skew the magnitude of associations, difficulties in establishing the time of occurrence of a

certain event or problems related to the collection of important confounders.

In conclusion, we described a large series of pSS patients who showed a 14.6% of FM, which was associated to the presence of constitutional, fatigue and arthralgia symptoms, splenomegaly, genital, skin and ear involvement, dyslipidaemia and higher SSDAI score. Fatigue symptoms were frequent in FM-pSS patients, but were not associated to higher activity scores when appeared without FM. Further studies to confirm the relationship between fatigue and pSS disease activity are needed.

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