

# Raynaud's Phenomenon in Primary Sjögren's Syndrome. Prevalence and Clinical Characteristics in a Series of 320 Patients

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**ABSTRACT. Objective.** To determine the prevalence of Raynaud's phenomenon (RP) in a large series of patients with primary Sjögren's syndrome (SS) and to identify the clinical and immunological features related to its presence.

**Methods.** In a cross sectional study, we investigated 320 consecutive patients with primary SS (294 women, 26 men; mean age at onset 60 yrs, range 16–87 yrs). All patients fulfilled 4 or more of the diagnostic criteria for SS proposed by the European Community Study Group in 1993. Diagnosis of RP in patients with SS was defined as intermittent attacks of digital pallor and/or cyanosis in the absence of any other associated disease or anatomical abnormalities.

**Results.** RP was present in 40 (13%) patients. All were women, with a mean age of 57 yrs (range 18–78). RP preceded onset of sicca symptomatology in 18 (45%) patients. The main triggering factor was exposure to cold, which induced RP in all patients, while emotional stress was a factor in 12 patients, as was job related predisposition in 2. Fifteen (38%) patients required pharmacological treatment with calcium channel blockers (12 patients) or angiotensin converting enzyme inhibitors (2 patients) during colder months, and one patient required treatment with intravenous prostacyclin for ischemic complications. Compared with SS patients without RP, those with RP showed a higher prevalence of articular involvement (50 vs 31%;  $p = 0.031$ ), cutaneous vasculitis (30 vs 11%;  $p = 0.003$ ), antinuclear antibodies (95 vs 65%;  $p < 0.001$ ), anti-Ro/SSA (59 vs 31%;  $p < 0.001$ ) and anti-La/SSB antibodies (44 vs 20%,  $p = 0.003$ ).

**Conclusion.** We found RP in 13% of patients with primary SS, in almost half of whom RP was the first autoimmune symptomatology. These patients constituted a subset of SS with a higher frequency of some extraglandular features and positive immunological markers. The clinical course of RP seems to be milder in patients with primary SS than in those with other systemic autoimmune diseases such as systemic sclerosis, with no vascular complications and pharmacological treatment needed in only 40% of patients. (J Rheumatol 2002;29:726–30)

## Key Indexing Terms:

RAYNAUD'S PHENOMENON

PRIMARY SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is an autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lachrymal glands<sup>1</sup>. In the absence of an associated systemic autoimmune disease,

patients with this condition are classified as having primary SS. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy)<sup>2</sup> to a systemic process with diverse extraglandular manifestations<sup>3–9</sup>. Due to this heterogeneity, attempts have been made to identify subsets of patients that would permit more reliable prediction of the disease course<sup>10–12</sup>.

Raynaud's phenomenon (RP) is a vascular disorder characterized by episodes of reversible digital ischemia in response to cold or stress. Affected individuals develop episodic digital ischemia usually defined as a triphasic color change with pallor followed by cyanosis and subsequently rubor. These 3 consecutive phases reflect the initiating vasospasm (pallor) causing deoxygenation of venous blood (cyanosis), and finally the reactive hyperemia (rubor) due to the blood return<sup>13</sup>. However, most investigators recognize that this full triphasic color change is not essential for the

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Submitted March 20, 2001; revision accepted October 5, 2001.

diagnosis of RP, and the European classification uses RP as a blanket term for all cold related vasospasm.

RP is generally classified as primary (in the absence of any associated process) or secondary if an associated disease (most frequently an autoimmune disease) or an environmental condition is present<sup>14</sup>. RP is a well known extraglandular feature described in patients with primary SS<sup>15-18</sup>, although its presence and clinical significance in patients with SS has been little studied<sup>19-21</sup>.

We investigated the prevalence and clinical characteristics of RP in a large series of patients with primary SS, and evaluated the correlation with clinical and immunological features of SS.

## MATERIALS AND METHODS

**Patients.** We investigated 320 consecutive patients (294 women, 26 men; mean age at onset 60 yrs, range 16–87 yrs) in our 2 institutions. All patients fulfilled  $\geq 4$  of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993<sup>22</sup>. No patient presented clinical or immunologic evidence of other systemic autoimmune disease. All patients underwent a complete history and examination, as well as diagnostic tests for SS applied according to the recommendations of the European Community Study Group<sup>22</sup>. We considered as exclusion criteria the existence of an associated systemic autoimmune disease, preexisting lymphoproliferative diseases, and hepatitis B, hepatitis C or human immunodeficiency virus infections.

Diagnosis of RP in patients with SS was defined as intermittent attacks of digital pallor and/or cyanosis in the absence of any other associated disease or anatomical abnormality. In patients with RP we evaluated the following characteristics: time of RP onset, the existence of triggering factors or cardiovascular risk factors, the distribution of vasospastic episodes in the different extremities, the existence of associated symptomatology (pain, tingling, swollen hands, sclerodactyly, telangiectasias) or vascular complications (digital ischemia, gangrene). We also analyzed the pharmacological treatment received.

**Laboratory studies.** Immunologic tests included antinuclear antibodies (ANA) (indirect immunofluorescence using mouse liver as substrate), antibodies to double stranded DNA (dsDNA; determined by Farr's ammonium sulfate precipitation technique), precipitating antibodies to the extractable nuclear antigens Ro/SSA and La/SSB (counterimmunoelectrophoresis), and rheumatoid factor (RF) (latex fixation and Waaler-Rose tests). Complement factors (C3 and C4) were estimated by nephelometry (Behring BNA nephelometer) and CH50 by the Lachmann hemolytic technique.

**Statistical analysis.** We used conventional chi-square and Fisher's exact test to analyze qualitative differences. For comparison of quantitative variables, Student t test was used in large samples of similar variance, and the nonparametric Mann-Whitney U test for small samples. A value of  $p < 0.05$  indicated statistical significance. The odds ratio (OR) was calculated for assessing the risk of appearance of each variable, with a confidence interval (CI) of 95%. This statistical analysis was performed with the SPSS programs using information stored in the database program.

## RESULTS

**Characteristics of RP in patients with SS.** We diagnosed RP in 40 (12.5%) of our patients with SS. All were women, with a mean age of 57 years (range 18–78 yrs). The main clinical features of RP are summarized in Table 1. RP preceded onset of sicca symptomatology in 18 (45%) patients, both conditions appeared simultaneously in 12 (30%), and RP

Table 1. Characteristics specific to RP in patients with SS.

	Patients with RP and SS, n = 40 (%)
RP onset	
Before SS onset	18 (45)
Simultaneous onset	12 (30)
After SS onset	10 (25)
Distribution of RP	
Hands	40 (100)
Only fingers	9 (23)
Toes	10 (25)
Associated symptomatology	
Tingling	19 (48)
Telangiectasias	14 (35)
Pain	10 (25)
Sclerodactyly	1 (3)
Digital ulcers	1 (3)
Color change	
Monophasic	6 (15)
Biphasic	13 (33)
Triphasic	21 (52)
Triggering factors	
Cold exposure	40 (100)
Emotional stress	12 (30)
Job related predisposition	2 (5)
Cardiovascular risk factors	
Dyslipidemia	4 (10)
Hypertension	8 (20)
Smoking	2 (5)
Menopausal status	21 (52)
Pharmacological treatment	
Calcium channel blockers	12 (30)
Angiotensin converting enzyme inhibitors	2 (5)
Prostacyclin	1 (3)
Altered capillaroscopy	5/10 (50)

appeared after sicca syndrome in the remaining 10 (25%). RP affected the fingers in all patients, and in 10 patients also affected the toes. The distal interphalangeal joints, proximal interphalangeal joints, and metacarpophalangeal joints were affected in 9 (22%), 11 (28%), and 20 (50%) patients, respectively. Other associated symptoms were tingling in 19 (48%) patients, telangiectasias in 14 (35%), digital pain in 10 (25%), and sclerodactyly in one (3%). One patient presented vascular complications (digital ulcers and distal gangrene).

The main triggering factor was exposure to cold, which induced RP in all patients, while emotional stress was a factor in 12 patients, as was job related predisposition in 2. Twenty-one patients presented the classic triphasic color change, 13 biphasic changes, and the remaining 6 monophasic changes. The duration of the attack ranged from 5 minutes to 4 hours, with a mean frequency of one attack per day during the winter. We detected the following cardiovascular risk factors: menopausal status in 21 patients, hypertension in 8, dyslipidemia in 4, and smoking in 2. Fifteen (38%) patients required pharmacological treatment

Table 2. Clinical and immunological characteristics of patients with primary SS, according to the presence or absence of RP.

	SS with RP n = 40 (%)	SS without RP n = 280 (%)	p
Females	40 (100)	254 (91)	—
Mean age, yrs ± SD	56.8 ± 13.9	60.4 ± 13.1	—
Xerostomia	38 (95)	272 (97)	—
Xerophthalmia	35 (88)	258 (92)	—
Parotidomegaly	12 (30)	47 (17)	—
Articular involvement	20 (50)	88 (31)	0.031
Cutaneous vasculitis	12 (30)	32 (11)	0.003
Peripheral neuropathy	5 (13)	21 (8)	—
Autoimmune thyroiditis	5 (13)	46 (16)	—
Renal involvement	6 (15)	19 (7)	—
Pulmonary fibrosis	8 (20)	28 (10)	—
Antinuclear antibodies	38 (95)	182 (65)	< 0.001
Rheumatoid factor	21 (53)	102 (36)	—
Anti-Ro/SSA antibodies	24 (60)	86 (31)	< 0.001
Anti-La/SSB antibodies	17 (43)	57 (20)	0.003
Hypocomplementemia	8 (20)	38/261 (15)	—
Cryoglobulins	7 (18)	25/211 (12)	—

with calcium channel blockers (12 patients) or angiotensin converting enzyme inhibitors (2 patients) during the colder months, and one patient required treatment with intravenous prostacyclin for ischemic complications.

Nailfold capillaroscopy was performed in 10 patients. Five (50%) had pathological findings, which were nonspecific in 4 patients (crossed capillaries), while in the remaining one scleroderma-type changes were observed (pericapillary hemorrhages).

Finally, we tested anticentromere (ACA) and anti-Scl-70 antibodies in 30 of the 40 patients with RP. Two patients showed positive ACA and none anti-Scl-70 antibodies. Both ACA+ patients showed altered nailfold capillaroscopy (crossed capillaries and pericapillary hemorrhages, respectively), although neither presented clinical features of systemic sclerosis (SSc). Interestingly, both patients showed

positive ANA with negative anti-Ro/SSA and anti-La/SSB antibodies.

**Correlation with clinical and immunological features of SS.** In those patients with SS and RP, the most common extraglandular manifestations were articular involvement (50%), cutaneous vasculitis (30%), pulmonary involvement (20%), renal involvement (15%), thyroiditis (13%), and peripheral neuropathy (13%). The most frequent immunological markers were ANA (95%), anti-Ro/SSA antibodies (59%), RF (53%), and anti-La/SSB antibodies (44%). Compared with patients without RP, those with RP showed a higher prevalence of articular involvement (50 vs 31%;  $p = 0.031$ , OR 2.18, CI 1.05–4.50), cutaneous vasculitis (30 vs 11%;  $p = 0.003$ , OR 3.32, CI 1.39–7.54), ANA (95 vs 65%;  $p < 0.001$ , OR 10.23, CI 2.54–88.96), anti-Ro/SSA (59 vs 31%;  $p < 0.001$ , OR 3.38, CI 1.63–7.16), and anti-La/SSB antibodies (44 vs 20%;  $p = 0.003$ , OR 2.89, CI 1.35–6.07) (Table 2).

## DISCUSSION

The prevalence of RP in our patients with primary SS was 13%, a lower figure than that observed in previous studies<sup>19–21</sup>, where prevalence ranged from 29 to 33% (Table 3). One possible explanation for this finding may be geographical, as colder climates might predispose the development of RP, in association with other possible risk factors<sup>23</sup>. Moreover, the different criteria used for the SS diagnosis may influence the prevalence of RP observed. In our study, if we analyzed the subset of patients who fulfilled Fox criteria<sup>24</sup>, we found a higher prevalence of RP (21%) than that found among patients classified by the European criteria (13%). In addition, Valter and Maricq<sup>25</sup> have shown that there is a significant difference in the prevalence of RP between 2 ethnic groups living in the same geographic region, suggesting that genetic factors may contribute to the predisposition to RP. We have studied the presence of RP in the largest series of SS yet analyzed, and found a higher

Table 3. RP in patients with primary SS: previous studies.

	Skopouli 1990 <sup>20</sup>	Youinou 1990 <sup>19</sup>	Kraus 1992 <sup>21</sup>	Present Study, 2001
Number of SS patients	110	45	104	320
Country	Greece	France	Mexico	Spain
SS criteria	Greek	Greek	Fox	European
Patients with RP (%)	36 (33)	15 (33)	30 (29)	40 (13)
Females (%)	ND	ND	ND	40 (100)
Mean age, yrs	55	58	51	60
RP precedes SS (%)	42	47	37	45
Clinical associations	Swollen hands	Arthritis	Arthritis, vasculitis, pulmonary fibrosis, parotidomegaly	Arthritis, vasculitis
Immunological associations	—	—	—	ANA, Ro/SSA, La/SSB
Vascular complications, %	0	ND	0	2

ND: no data.

prevalence of RP in patients with primary SS than in the healthy Spanish population (3.7%)<sup>26</sup>, although the ideal would have been a comparison with matched patients with primary RP living in the same geographical area. All our 40 patients with SS and RP are women, a predominance suggested by other studies<sup>10,27</sup>.

We found that RP was the first clinical feature, preceding sicca symptomatology, in almost 50% of our patients. This finding, suggested by other studies<sup>19-21</sup> that found percentages ranging between 37 and 47% (Table 3), is interesting, as RP may be considered one of the first manifestations of SS, detectable in the early stages of the disease. Some authors have discovered subclinical but histologically proven SS in patients with RP of less than 5 years' duration<sup>28</sup>.

Analysis of the clinical features of the subset of patients with SS and RP showed a higher frequency of the main extraglandular features of SS, specifically cutaneous and articular involvement. Youinou, *et al*<sup>19</sup> and Skopouli, *et al*<sup>20</sup> have suggested that SS patients with RP tend to develop more systemic features than those without RP, although without significant differences. Kraus, *et al*<sup>21</sup> described a higher frequency of articular, cutaneous, and pulmonary involvement in patients with SS and RP, and Foster, *et al*<sup>29</sup> found a higher frequency of arthritis. These reports show a pattern of SS expression very similar to that of our patients with SS, suggesting that patients with SS and RP constitute a subset with a homogeneous clinical presentation, probably related to a specific genetic background that could explain the differences observed between both groups of SS patients. Indeed, some studies have described an association with HLA-DR3 and DR4 of RP in SS<sup>29,30</sup>.

Although similar studies found no correlations with the immunological measures<sup>19-21</sup>, we found a higher frequency of immunological markers in our SS patients with RP, mainly ANA and anti-Ro/SSA. Our RP patients showed a higher frequency of associated extraglandular features, most of which are closely related to positive immunological markers, especially with anti-Ro/SSA antibodies<sup>31-33</sup>. Nevertheless, some of our RP patients showed positive ANA with negative anti-Ro/La antibodies, and interestingly, in these ANA+/ENA- patients we identified 2 with positive ACA. The clinical significance of ACA in patients with primary SS has been little studied, and none of the main studies that analyze RP in primary SS tested ACA in its patients with RP<sup>19-21</sup>. Some studies have described the existence of a small number of SS patients with positive ACA. Tubach, *et al*<sup>34</sup> described 8 ACA+ patients without RP or SSc, 4 of whom had primary SS. Caramaschi, *et al*<sup>35</sup> analyzed 10 SS patients positive for ACA and found a higher frequency of RP and a lower frequency of anti-Ro/SSA. Of note, 4 of these patients developed limited SSc during the followup, while in the remaining 6 the diagnosis of primary SS was unchanged. Thus, we recommend testing

for ACA in patients with primary SS and RP, especially in those cases with positive ANA with negative anti-Ro/La antibodies. SS patients with RP need closer followup, with attention to the possible development of clinical features of SSc, mainly dermatological and pulmonary manifestations.

We performed nailfold capillaroscopy in 10 of our RP patients, and found microvascular abnormalities, mainly non-specific findings, in half. Recently, Tektonidou, *et al*<sup>36</sup> described capillaroscopic abnormalities in 16 patients with SS and RP. Only 2 (12.5%) had a normal pattern, while 12 (75%) showed nonspecific findings (mainly crossed capillaries) and the remaining 2 (12.5%) showed scleroderma-type findings. However, it should be noted that half of their SS patients without RP also showed nonspecific findings. The usefulness of nailfold capillaroscopy in SS patients may lie in the identification of patients with other sclerodermic findings, such as sclerodactyly, telangiectasias, or positivity for ACA<sup>37</sup>, who may represent a subset of "primary" SS patients with a subsequent evolution to SSc, or patients with an overlap syndrome.

Another interesting finding of the study is that RP in patients with primary SS did not induce significant local sequelae such as digital ulcers or gangrene, in contrast to SSc, where RP is often associated with serious local problems<sup>38</sup>. Other studies also did not find local sequelae in SS-RP patients (Table 3), although Skopouli, *et al* found<sup>20</sup> swollen hands and evidence of small soft tissue calcifications more frequently in SS patients with RP.

We found Raynaud's phenomenon in 13% of patients with primary Sjögren's syndrome, with RP being the first autoimmune symptomatology in almost 50% of these. Patients with RP constituted a subset of SS patients with a higher frequency of some extraglandular features and positive immunological markers. The clinical course of RP seems to be milder in primary SS than in other systemic autoimmune diseases such as systemic sclerosis, with no vascular complications and needing pharmacological treatment in only 40% of patients.

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