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# Prospective evaluation of frequency of signs of systemic sclerosis in 76 patients with morphoea

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## ABSTRACT

**Objective.** Some authors consider that morphoea and systemic sclerosis (SSc) could be part of the same disease spectrum. The aim of this study was to analyse the prevalence of signs indicative of SSc in a cohort of patients with morphoea.

**Methods.** This is a prospective multi-centre study performed in four French academic dermatology departments: 76 patients with morphoea and 101 age- and sex-matched controls, who underwent complete clinical examination, were enrolled. A systemic search for signs indicative of SSc (e.g. Raynaud's phenomenon, reflux) was performed with the help of a standardised questionnaire.

**Results.** There were 58 women and 18 men (ratio = 3/1) with a median age of 59 years. Mean age at diagnosis was 54 years (extremes, 13–87). 49 subjects had plaque morphoea, 9 had generalised morphoea and 18 had linear morphoea. Mean duration of morphoea was 7.9 years. Signs possibly indicative of SSc were noted in four patients of the control group and in 8 patients with morphoea. This difference was not statistically significant ( $p=0.129$ ). Further investigations ruled out SSc in all patients.

**Conclusion.** Signs indicative of SSc are statistically not more frequently present in patients with morphoea than in controls and this study does not support the view that those 2 entities are part of a common disease spectrum.

## Introduction

The clinical spectrum of many of the connective tissue diseases ranges from isolated cutaneous involvement to systemic disease involving many organs. For example, lupus erythematosus can affect only the skin in some patients, while others will develop significant systemic disease with renal, cardiac,

neurologic and serosal involvement. In the former case, we refer to “cutaneous lupus erythematosus” and in the latter to “systemic lupus erythematosus” (1). And clearly, there is a continuous spectrum between those 2 entities, as it's not possible, initially, to distinguish between the patients who will only have cutaneous involvement and those who will develop systemic disease, nor is it possible to predict to what extent systemic manifestation will occur. The same is true for dermatomyositis, and there is a continuous spectrum between the patients that have only the typical cutaneous involvement – and to which we refer as “amyopathic dermatomyositis” – and those who have slight, intermediate or significant muscular involvement or interstitial lung disease (2).

Many physicians apply the same parallelism to patients with morphoea, also called “localised scleroderma”, in regard to its potential evolution into systemic sclerosis (SSc). They consider that morphoea is part of the spectrum of SSc (also called scleroderma) and that some patients are at risk and will develop the full blown spectrum of the disease.

Though patients with morphoea have significantly more often than controls biological stigmata of auto-immunity (3), and they have probably an increased risk of developing auto-immune disorders in general, we do not believe that patients initially diagnosed as having morphoea will evolve specifically into SSc. Furthermore, the dermatologic signs in patients with cutaneous and systemic lupus erythematosus or those with amyopathic and classic dermatopolymyositis are the same. However, this is not true in patients with morphoea and SSc, though they share the same histopathologic findings under the microscope. The former have indurated and discoloured

circumscribed plaques while the latter develop diffuse acral induration beginning on the hands.

Thus, the aim of this study was to search systematically for clinical signs of SSc in a cohort of patients with morphoea.

### Material and methods

This is a prospective multicentre study. Patients were recruited from November 2008 to June 2010 in the departments of dermatology from 4 French university hospitals: Strasbourg, Montpellier, Tenon Hospital Paris and Henri Mondor Hospital Créteil.

Patients were included if the diagnosis of morphoea was confirmed clinically by an experienced dermatologist or after a skin biopsy. Data were collected on a standardised questionnaire and included age, sex and associated clinical findings such as Raynaud's phenomenon (RP), telangiectasia, visible nail fold capillaries, sclerodactyly, digital ulcers or scars, sicca syndrome, crackles on lung auscultation, dyspnea and signs indicative of gastro-oesophageal reflux. The various forms of morphoea were specified. The number of plaques, their size, their location, their clinical description and the functional consequences were reported. When a patient had both plaque morphoea and linear lesions, he was classified as having linear morphoea. If clinical signs indicative of SSc were present, investigations were completed with blood tests, lung function tests and morphological evaluations. Patients had capillaroscopy or nailfold examination with a handheld dermatoscope by an experienced clinician. Diagnosis of scleroderma was established if the patient fulfilled the preliminary American College of Rheumatology (ACR) classification criteria for SSc (4); when this study was performed, the combined ACR/EULAR 2013 criteria (5) were not published.

In order to assess exact relevance of each individual clinical finding (as for example regurgitation or RP), we compared their frequency to a group of control patients. We recruited sex- and age-matched controls who were seen in the dermatology department for a reason other than morphoea and/

or SSc and who had a complete skin and mucosal examination. The majority of control patients were followed up for cutaneous cancers, mainly stage I melanoma. Table I provides the details of the controls included in this study. Statistical analyses were performed in collaboration with the department of Biostatistics. The frequency of findings between cases and control group was compared using Fisher's exact test for count data.

Under French law, this type of study, which does not involve any invasive investigation but relies on a questionnaire performed during a regular consultation, does not need the approval of the institutional review board.

### Results

#### Epidemiology

We included 76 patients with morphoea. This group consisted of 18 men (24%) and 58 women (76%). The mean age was 54 years (extremes, 13–87). The mean duration of morphoea was estimated to 7.9 years (extremes, 6 month–36 years), but it was not specified in 46 cases. The diagnosis was made on typical clinical findings in 50 patients and was confirmed by a biopsy in 26.

Forty-nine patients had plaque morphoea, 18 had linear morphoea and 9 had generalised morphoea.

One hundred and one subjects were included in the control group. They were 68 women and 33 men. The mean age was 57 years (extremes, 1–87 years). There is no significant statistical difference between the patients and the control group for the age ( $p=0.44$ ) and the sex ( $p=0.30$ ). Details about reasons for consultation are provided in Table I.

#### Signs of systemic sclerosis

Signs possibly indicative of SSc were noted in four patients of the control group and in 8 patients with morphoea. The difference is not statistically significant ( $p=0.129$ ). The 8 patients with morphoea respectively had: RP in three cases, acrosclerosis in two cases, perioral telangiectasia in one case, regurgitation in one case and subcutaneous calcinosis in one case. None of the patient had signs indicative of lung involvement. The patient with subcutaneous

**Table I.** Details of controls included in the study.

| Disease   | Number of patients |
|---|--------------------|
| Skin cancer follow-up and screening for skin cancer | 63                 |
| Lupus erythematosus                                 | 5                  |
| Psoriasis   | 4                  |
| Vasculitis <sup>1</sup>                             | 4                  |
| Lichen planus                                       | 3                  |
| Sarcoidosis   | 3                  |
| Cutaneous infections <sup>2</sup>                   | 5                  |
| Venous insufficiency                                | 2                  |
| Miscellaneous <sup>3</sup>                          | 12                 |
| TOTAL   | 101                |

<sup>1</sup>One patient with each of the following entities: eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, polyarteritis nodosa and leucocytoclastic vasculitis.

<sup>2</sup>2 patients with cutaneous abscesses, 2 patients with herpes simplex infection and 1 patient with erythema migrans

<sup>3</sup>One patient with each of the following entities: acne, pityriasis rubra pilaris, alopecia, aphthous stomatitis, granuloma annulare, porphyria cutanea tarda, pruritus, irritative dermatitis, Sneddon syndrome, drug reaction, hidrosadenitis suppurativa, HIV infection.

calcinosis had a dimelic linear morphoea of lower limbs and a type 1 diabetes. She was 57 years old, the disease evolved since the age of 11 years. She had never developed any other clinical or biological signs of SSc. One patient with RP and the 2 patients with acrosclerosis had generalised pansclerotic morphoea. Echocardiography and lung function tests with DLCO were normal in those patients, except for restrictive pneumopathy. Acrosclerosis occurred in the context of generalised pansclerotic morphoea and respected fingertips. Patients did not develop ulceration or acral scarring. Another patient with RP had linear morphoea. Dermatoscopic examination of nailfold capillaries was unremarkable.

In the control group, we noted RP (2), telangiectasias (2) and esophageal reflux (1). The patients with RP and telangiectasia had ANCA+ vasculitis.

Further investigations including capillaroscopy, chest CT scan, functional lung testing with DLCO ruled out SSc in the patients. No other clinical sign of SSc was noted in the patient with esophageal dysmotility.

Laboratory analyses were performed in 36 patients with morphoea. Twenty-

eight patients with morphoea had anti-nuclear antibodies (ANA) superior to 1/160. Only one of the tested patients had anti-centromere (and he was found to have primary biliary cirrhosis) without anti-Scl70 or anti-RNA polymerase III antibodies. Rheumatoid factor was assessed in 25 patients with morphoea and they were present in 15 patients with a titer ranging from 20 to 62 UI/ml in enzyme-linked immunosorbent assay.

## Discussion

This prospective study shows that clinical signs indicative of SSc were statistically not more frequent in patients with morphoea than in a control group. None of the patients with morphoea evolved into SSc after a mean disease duration of almost 8 years. This message is furthermore supported by the fact that many patients included in this study had very severe or widespread morphoea, as a consequence of a recruitment bias related to the fact that only patients seen in tertiary referral centres were included. This explains for example the high percentage of patients (11%) with generalised morphoea.

Patients with the fibrosing dermal conditions morphoea and lichen sclerosus are prone to autoimmunity in general, but not specifically to SSc. Indeed, antinuclear antibodies are found more frequently in patients with those conditions than in controls (3). In patients with linear morphoea, a potentially severe form of the disorder, often starting in childhood, their presence and titer seems to correlate to gravity (3). Extracutaneous involvement of muscles, bones and/or central nervous system can occur in this variant, but manifestations are clearly different from those occurring in patients with SSc (6-9). There are some rare published reports of co-occurrence of morphoea and SSc (10, 11), but this combination seems not more frequent than co-occurrence of morphoea with other connective diseases (12-17) or auto-immune cytopenias (18-20).

Morphoea is also called "localised scleroderma". That might explain why many physicians believe that localised scleroderma and systemic scleroderma are the two ends of a continuous spectrum. This study does not support this

assumption. Though morphoea and SSc are often undistinguishable under the microscope, clinical features and prognosis are very different. For instance, acral sclerosis, the hallmark of SSc, the importance of which was underlined in the recently published ACR/EULAR diagnostic criteria (5) of this entity, is absent in morphoea. Pulmonary involvement, reflux disease or cardiac involvement, classic complications of SSc, do not occur in morphoea. In times of immediate accessibility to information for patients through the Internet, we consider that the name "localised scleroderma" is a misnomer, as many patients will find information relating to SSc. We consider that there is no overlap between the 2 conditions morphoea and SSc; patients with morphoea have probably an increased risk to develop autoimmune conditions in general, but not specifically SSc. The term localised scleroderma should be abandoned and this condition should only be referred to as morphoea. In a previous study, we already demonstrated that patients with morphoea are however at increased risk of developing genital lichen sclerosus (21) and thus a complete clinical examination by a dermatologist at least once a year is indicated.

## Key message

- This study does not support the idea that morphoea and systemic sclerosis are part of a related disease spectrum

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