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Prospective capillaroscopy-based study on transition from primary to secondary Raynaud's phenomenon: preliminary results

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SUMMARY

The objective of this prospective study was to investigate the transition from primary (PRP) to secondary (SRP) Raynaud's phenomenon (RP), in a large cohort of patients affected by isolated RP.

A total of 2065 patients with RP were investigated by clinical interview, laboratory examinations, and nailfold videocapillaroscopy (NVC). Patients with negative NVC at first visit were yearly followed to monitor either the appearance of specific morphological alterations at NVC, or clinical manifestations of an underlying disease. Capillary abnormalities at NVC were scored, as well as the qualitative patterns of microangiopathy (*Early*, *Active* and *Late*).

NVC was found negative at first visit in 1500 subjects; among them, 412 patients were evaluable and they were followed for a mean time of 5±4 years (range 2-13 years). Sixty-eight patients (16%) achieved a diagnosis of SRP during follow-up, showing normal or not specific capillary alterations at NVC 4% of patients (the diagnosis was undifferentiated connective tissue diseases), *Early* scleroderma-pattern 57%, *Active* scleroderma-pattern 7%, *Late* scleroderma-pattern 12%, and scleroderma-like pattern 18% of patients. The time of transition from normal/not specific capillary alterations to *Early* scleroderma-pattern was 4.4±3.8 years. Enlarged capillaries (diameter between 20 and 50 microns) and mild reduction of capillary density were found the more frequent markers at first NVC visit in patients who progressed to a scleroderma pattern (P=0.01).

This study demonstrates in a large cohort, that almost 16% of patients initially diagnosed as affected by RP with negative NVC may transit to SRP during a mean follow-up of 4.4 years. PRP patients showing major not-specific alterations of nailfold capillaries at first NVC should be strictly monitored at least once a year since at higher risk of transition to SRP.

Key words: *Raynaud phenomenon, Systemic sclerosis, Nailfold videocapillaroscopy, Microangiopathy.*

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INTRODUCTION

Raynaud's phenomenon (RP) is an exaggerate vasomotor response to temperature changes or emotional factors. It is mainly localized to the distal portion of the finger but also toes, nose and ears can be affected. It consists of three phases: ischemic, cyanotic and reactive hyperhemia (1). The etiology as well as the pathophysiology of the disease have not been completely established (1).

RP is classified as primary (PRP) or secondary (SRP). The diagnosis of PRP is due to normal capillaroscopy, negative or normal laboratory tests including anti-nuclear antibodies (ANA) and inflammatory parameters, symmetrical distribution of the phenomenon, absence of skin ulcers, absence of underlying disease (2, 3). PRP may be present in 5% of healthy subjects with prevalence for females (4).

Reports on the rate of transition from PRP to SRP (identified by diagnosis of an associated disease) vary widely.

The incidence as well as the prevalence of SRP also seem to depend on the origin of the patient sample (5).

Despite the inconsistencies, the rate of this transition is high enough to make follow-

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up studies of clinical interest. Several risk factors for transition from PRP to SRP have been implicated, but there is still a lack of adequate prognostic evidence regarding the course of the disease.

In 2006 Hirshl et al. investigated a clinical sample of outpatients with RP. They demonstrated the suitability and usefulness of systematic diagnostic screening and thorough follow-up.

With such an approach, 11% of patients initially diagnosed as having primary RP were found to have transitioned to either suspected SRP or confirmed SRP during the follow-up period of >10 years (5). Cutolo et al. in 2007 demonstrated that during a follow-up period of 11.2±3.9 years the incidence of SRP shifted to 14.9%, in patients initially diagnosed as having PRP. A careful analysis by nailfold video capillaroscopy (NVC) showed a similar incidence of SRP (14.6%), but after a much shorter follow-up (29.4±10 months) (6).

NVC is a tool that increases our ability to distinguish between primary and secondary RP, and allows early diagnosis of systemic sclerosis (SSc) and related scleroderma-spectrum disorders through recognition of the *early* scleroderma-pattern of microangiopathy (7, 8).

As a matter of fact, specific microvascular alterations are recognized by capillaroscopic analysis also in several different connective tissue diseases other than SSc (*i.e.*, dermatomyositis, mixed connective tissue disease and systemic lupus erythematosus) (9).

In addition, distinct morphologic NVC patterns and a significant and gradual increase of microvascular abnormalities are observed during the progression of SSc, reflecting the evolution of the pathophysiologic process (10).

The aim of this prospective study was to investigate by NVC predictive abnormalities and timing of transition from PRP to SRP in a large cohort of patients affected by isolated RP, consecutively recruited from *Rheumatologic Service for the Diagnosis and Management of Vascular and Connective Tissue Disease* of University of Genova during the years 1999-2011.

MATERIALS AND METHODS

A total of 2.065 patients with RP were investigated by clinical interview, laboratory examinations (inflammation parameters and autoantibodies) and NVC.

Patients achieving a diagnosis of RP with negative NVC at first visit were yearly followed for a mean time of 5±4 years, to detect both the possible transition to SRP and the appearance of specific nailfold capillary abnormalities.

All patients gave informed consent to enter the observational study.

Appearance of diagnostic alterations at NVC, specific autoantibodies positivity, or clinical manifestations of a connective tissue disease were investigated at each follow-up visit to detect the transition to SRP (11).

Nailfold microangiopathy was investigated by NVC: capillary abnormalities were scored, and the qualitative patterns of microangiopathy *early*, *active* or *late* classified, if present, as previously reported (10, 12).

Nailfold capillary alterations with the features of the scleroderma-pattern, but non classifiable into the *early*, *active*, or *late* pattern, were classified as *scleroderma-like* pattern (8).

The frequency of nailfold capillary abnormalities in patients that transited from PRP to SRP was also investigated.

RESULTS

A diagnosis of SRP was obtained at first visit in 565 (27%) patients out of 2.065. Conversely, a diagnosis of RP with negative NVC was achieved at first visit in 1.500 subjects; among them, 1088 patients were lost during follow-up, or not prospectively evaluable. 412 patients were evaluable and they were followed for a mean time of 5±4 years (range 3-13 years). Mean age of patients included in the follow-up was 45±15 years, and duration of Raynaud's phenomenon was 9±9 years.

Sixty-eight patients with RP and negative NVC (16%) achieved a diagnosis of SRP

Table I - Outcome of capillary findings at nailfold videocapillaroscopy in patients with Raynaud's phenomenon that either transit or not to secondary Raynaud's phenomenon.

	RP diagnosis at first visit	Transition to SRP	No transition to SRP
	No. patients	No. (%) patients	No. (%) patients
Baseline NVC	412	68 (17)	344 (83)
Normal	73	8 (11)	65 (89)
Not-specific capillary alterations	339	60 (18)	279 (82)

RP, Raynaud's phenomenon; SRP, secondary Raynaud's phenomenon; NVC, nailfold videocapillaroscopy.

during follow-up. 344 subjects (84%) did not transit to SRP, and at the last visit of the study they were still showing a PRP with normal on not specific capillary alterations at NVC (Tab. I).

At last visit, in patients who switched to SRP, NVC was found normal or with not specific alterations in 5% of patients [the diagnosis was undifferentiated connective tissue diseases (UCTD), according to Mosca criteria 1999] (13), *early* scleroderma-pattern in 58% (the diagnosis was SSc, according to either LeRoy criteria 2001-23 patients, or according to preliminary criteria for the very early diagnosis of SSc - 16 patients) (11, 14), *active* scleroderma-pattern in 7% (the diagnosis was SSc), *late* scleroderma-pattern in 12% (the diagnosis was SSc), and *scleroderma-like* pattern in 18% of patients [this last group included patients with diagnosis of mixed connective tissue diseases (MCTD) or UCTD] (Fig. 1).

The time of transition from normal/not specific capillary alterations to *early* scleroderma-pattern was 4.4±3.8 years.

Enlarged capillaries (diameter between 20 and 50 μm) and mild reduction of capillary density were found the more frequent markers at first NVC visit in those RP patients who progressed to a scleroderma pattern (Tab. I).

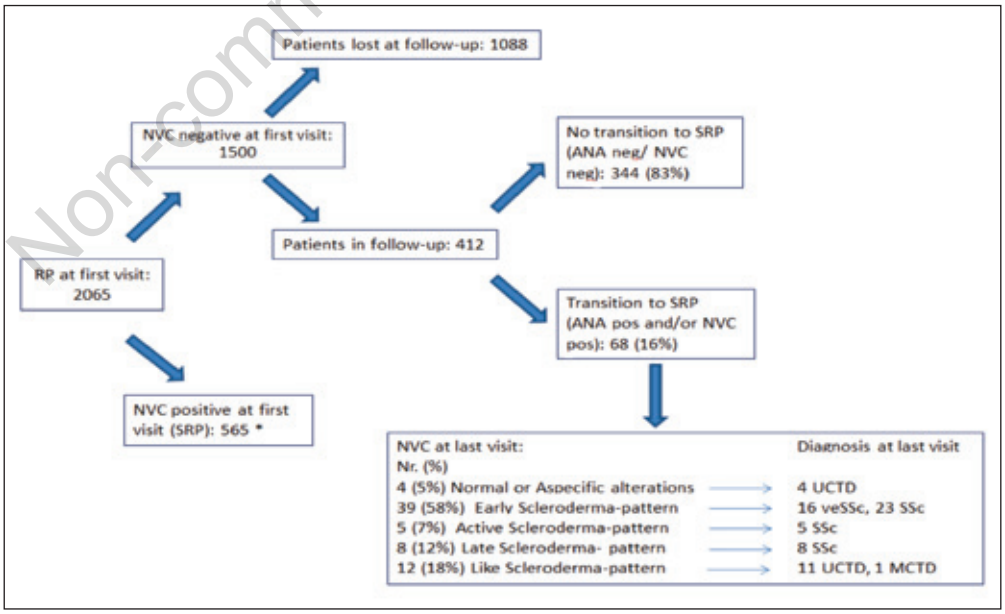

Figure 1 - Outcome of patients with Raynaud's phenomenon (RP) yearly followed by clinical examination, laboratory tools and nailfold videocapillaroscopy (NVC) over the time (average 5±4 years). Both NVC and clinical outcomes are also reported. PRP, primary Raynaud's phenomenon; SRP, secondary Raynaud's phenomenon; ANA, anti-nuclear antibodies; UCTD, undifferentiated connective tissue diseases; MCTD, mixed connective tissue diseases. *Patients not matter of present study.

DISCUSSION AND CONCLUSIONS

Our work, conducted in a large cohort, demonstrates that almost 16% of patients initially diagnosed as affected by RP with negative NVC may transit to SRP when carefully prospectically evaluated by clinical and laboratory examinations and nailfold videocapillaroscopy. Transition occurs during a mean follow-up of 4.4 years. Subjects with major not-specific alterations, as reduced number of capillaries and increased diameter of nailfold capillaries at first NVC have more transition probabilities, as recently reported (15). Therefore these PRP patients should be strictly monitored at least once a year since at risk of transition to SRP.

As previously observed it is very important to assess early signs, risk factors and rate of transition from primary PRP to SRP (5). Hirshl study's demonstrated that patients diagnosed initially as having PRP may actually comprise 1 of 3 groups: those with idiopathic RP (signs of an underlying disease for >10 years), those with a rather benign disease course, characterised by earlier presentation to a specialist, initial presence of an abnormal result on a thoracic outlet test, earlier occurrence of abnormal findings during follow-up (in particular, high ANA titer with positivity for specific serologic ANA subsets) and an overall higher number of abnormal findings occurring in shorter sequence (more severe course of the disease) and those with a less severe course of the disease with much later onset of abnormal findings that remain stable for long periods of time and did not allow for a definite diagnosis. We have also to remind that in many cases these abnormal findings might be related to aging and have no direct implication regarding an underlying disease (a rather benign disease course) (5). The comparison between Hirshl and Cutolo's studies showed that diagnosis of the transition from PRP to SRP should be sup-

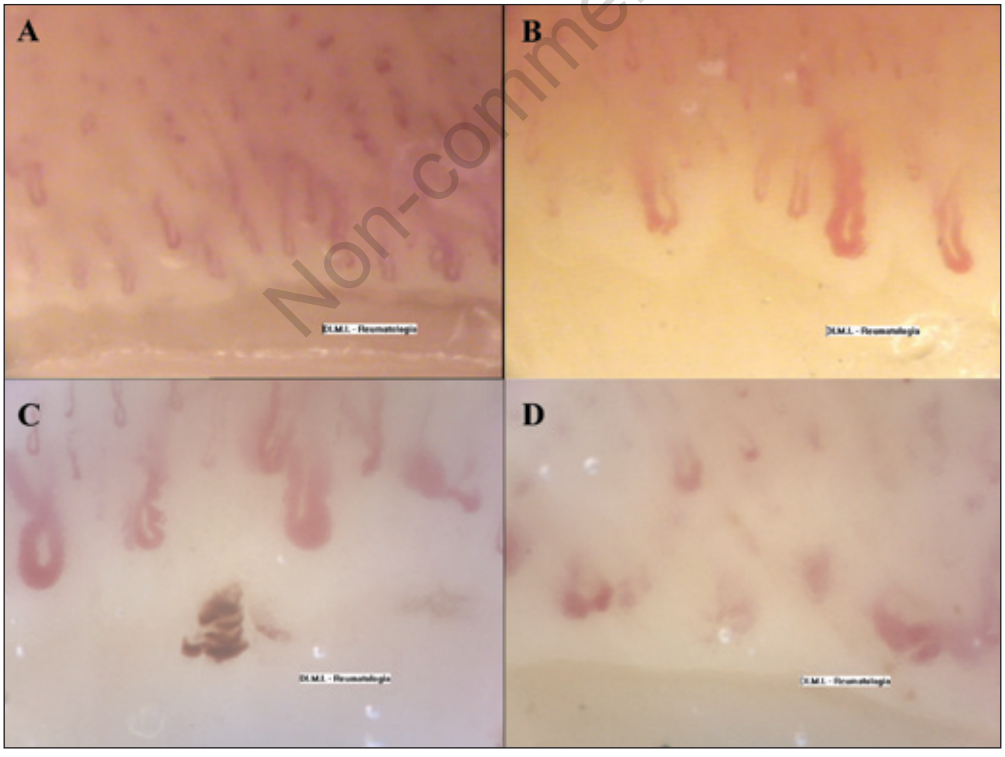

Figure 2 - Example of evolution of capillary findings in patient (M.O.) showing non-specific capillary alteration at nailfold videocapillaroscopy at A) first visit (25/2/1999), and transition to B) early (18/05/2003), C) active (21/11/2007) and D) late scleroderma pattern (19/02/2012).

ported by both clinical/laboratory parameters and identification of nailfold microvascular changes by capillaroscopy. However, whereas >90% of SSc patients and 85% of patients with MCTD present with RP as an early symptom (as also noted by Hirschl and colleagues), detection of the scleroderma-pattern (or the scleroderma-like pattern in the case of MCTD and dermatomyositis) by NVC allows a definite differential diagnosis between primary and secondary RP (6). Conclusion was that patients with PRP should undergo a careful semiannual capillaroscopic analysis in order to detect, at the earliest time and in the most reliable manner, the possible transition to SRP (6).

Of interest, our study confirms the transition from the *Early* to other NVC pattern of microangiopathy in SSc patients, as recently demonstrated (10). Thirteen out of 52 patients transit from *early* to either *active* or *late* pattern of microangiopathy after the diagnosis of SRP (see the example of patients M.O. in Fig. 2).

SSc is characterized by early and progressive microcirculatory impairment, which is associated with functional and organic clinical manifestations (16). In particular, SSc microangiopathy is a dynamic and sequential process, evolving from early enlargement of capillaries (giant capillaries) to capillary loss, and finally, to reactive neoangiogenesis (capillary ramifications) (10, 16). Scleroderma NVC patterns reflect the evolution of SSc microangiopathy and their recognition might be useful in assessing microvascular damage in individual patients, both at a single point in time and longitudinally. It is also recommended that patients with systemic sclerosis exhibiting rapid progression from the *early* to the *active* NVC pattern (<1 year) should be monitored closely, since the evidence suggests that they are at risk of rapid progression to the advanced (*late*) NVC pattern of microangiopathy that is associated with further clinical manifestations of SSc (10).

The high number of patients lost in follow-up might have implied a selection bias for patients who came back for follow-up visits, as it is possible that the latter had more bothering symptoms than those lost in follow-up. However, this might interfere with the percentage of patients who transited to SRP, but probably not influence the identification of predictive NVC capillary alterations.

Information concerning specific autoantibodies is not reported in this paper, as this is matter of ongoing report comprehensive of all clinical information. However, previous studies demonstrate that ANA positivity compared with NVC positivity have a different weight in decision making for follow-up of RP patients (15).

In conclusion, RP patients with negative NVC at first visit may transit to SRP during followup, displaying a nailfold scleroderma-pattern of microangiopathy, and NVC is confirmed an investigative method useful for the early diagnosis of SRP and related diseases, specially connective tissue disease such as systemic sclerosis.

Conflict of interests: the Authors declare no potential conflict of interests.

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