

## Connective tissue disease in patients presenting with Raynaud's phenomenon alone

Raynaud's phenomenon, first described by Maurice Raynaud in 1888,<sup>1</sup> is characterised by attacks of digital pallor due to constriction of small arteries or arterioles on exposition to cold or, less commonly, emotional stimuli. The white discoloration is followed by a cyanotic phase, resulting from stagnated blood flow in dilated capillaries and venules. Reactive hyperaemia, probably produced by local accumulation of vasodilating agents in ischaemic tissue, causes rubor on warming up. The cause of Raynaud's phenomenon is largely unknown. It has been reported to occur in some 10% of the population, especially in young women, and clusters in certain families.<sup>2</sup> It follows a benign course in most cases and may improve or even disappear in time. Raynaud's phenomenon, however, may also be a sign of connective tissue diseases. It is present in 95% of patients with scleroderma, 91% of patients with mixed connective tissue disease, 40% of patients with systemic lupus erythematosus, and is often seen also in patients with Sjögren's syndrome, dermatomyositis/polymyositis, and rheumatoid arthritis. In contrast with most cases in the population with an idiopathic or primary Raynaud's phenomenon, Raynaud's phenomenon is considered secondary to the connective tissue disease in these latter cases. It appears, however, as the first sign in 70% of patients with scleroderma, and may precede the development of this disease by many years. The same holds true for Raynaud's phenomenon in mixed connective tissue disease and, to a lesser extent, in systemic lupus erythematosus. Thus patients presenting with Raynaud's phenomenon alone may be in the early stages of a connective tissue disease. It is important for the rheumatologist confronted with a patient presenting with Raynaud's phenomenon to be aware of its significance as an early sign of a (developing) connective tissue disease, and to be familiar with the prognostic factors in primary Raynaud's phenomenon for the evolution to connective tissue disease. This should be the base for the clinical approach to the patient presenting with Raynaud's phenomenon alone.<sup>3</sup>

What do we know about the evolution from non-secondary Raynaud's phenomenon to connective tissue disease? Some years ago we followed up 64 patients with non-secondary Raynaud's phenomenon—that is, patients with primary Raynaud's phenomenon ( $n=30$ ) and patients with Raynaud's phenomenon and one or more symptoms of connective tissue disease but not fulfilling criteria for a specific connective tissue disease ( $n=34$ ), for six years.<sup>4</sup> The patients were all referred because of their Raynaud's phenomenon. During these six years 39 patients showed a stable course. The remaining 25 patients had an insidious progression towards connective tissue disease, in particular towards the limited cutaneous subset of systemic sclerosis.<sup>5</sup> Progression occurred more commonly (50%) in the group of patients with symptoms of connective tissue disease already at the onset than in patients with truly primary Raynaud's phenomenon at the start of the study (27%). These data fully compare with the retrospective study of Gerbracht *et al*<sup>6</sup> and largely with the prospective study of Fitzgerald *et al*,<sup>7</sup> who both studied patients with Raynaud's phenomenon referred to the clinic. In these latter patients asymptomatic signs and serological markers of connective tissue disease are often present.<sup>8</sup> Follow up data from patients with Raynaud's phenomenon in the general population are quite different as is shown by the low incidence or absence of connective tissue disease in a group of patients with Raynaud's phenomenon, probably more representative for

the general population, who were followed up primarily by questionnaire.<sup>9</sup> Thus a substantial number of patients referred to a rheumatologist because of their Raynaud's phenomenon will develop a connective tissue disease. This underlines the importance of selecting patients with Raynaud's phenomenon who are at risk for developing a connective tissue disease.

Which items have prognostic significance in primary Raynaud's phenomenon for the evolution to connective tissue disease? Firstly, the age of onset of Raynaud's phenomenon is important. In a previous study we found that the median age of onset in patients with primary Raynaud's phenomenon was 14 years, whereas it developed at a median age of 37 years in the patients with Raynaud's phenomenon and (symptoms of) connective tissue disease.<sup>8</sup> In only 24% of the patients with primary Raynaud's phenomenon did the phenomenon develop after the age of 20, whereas in 70% of patients with (symptoms of) connective tissue disease it developed after that age. Thus a relatively older age at onset should arouse the suspicion of an underlying or developing connective tissue disease. Secondly, the severity of Raynaud's phenomenon at presentation has prognostic significance. Measuring the severity of Raynaud's phenomenon by photoelectric plethysmography of the fingers during cooling and rewarming,<sup>10</sup> we found that patients with (symptoms of) connective tissue disease had a more severe Raynaud's phenomenon than patients with primary Raynaud's phenomenon. In addition, the degree of severity correlated with the number of affected organs.<sup>8</sup> Thirdly, the presence of antinuclear antibodies at presentation is a prognostic factor. In our group of patients antinuclear antibodies were present in 28% of patients with primary Raynaud's phenomenon, usually in low titre, whereas 80% of patients with Raynaud's phenomenon and (symptoms of) connective tissue disease were positive for antinuclear antibodies, in most cases in high titre.<sup>8 11</sup> The antigenic specificities of the antinuclear antibodies had prognostic value for the development of specific syndromes: anticentromere, directed against the CENP-B antigen, for limited cutaneous scleroderma including CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia), and anti-topoisomerase 1, also known as anti-Scl-70 or anti-Scl-86, for (diffuse) scleroderma.<sup>4 12 13</sup> Finally, nailfold capillary microscopy might be a tool for the early detection of connective tissue disease in patients with Raynaud's phenomenon. It discloses loss of capillaries and dilated and deformed capillaries in patients with Raynaud's phenomenon and (symptoms of) connective tissue disease, whereas capillary patterns are normal in patients with primary Raynaud's phenomenon.<sup>14-16</sup> Loss of nailfold capillaries may be considered as a local manifestation of a more generalised vasculopathy as suggested by the correlation between the reduction in the number of capillaries in the nail fold and the decrease of the pulmonary diffusing capacity in patients with Raynaud's phenomenon with and without an underlying connective tissue disease.<sup>17 18</sup> The predictive value of nailfold capillary microscopy for the development of connective tissue disease has been suggested,<sup>19 20</sup> but has to be confirmed by long term prospective studies.

What are the consequences of these findings for the investigation of patients presenting with Raynaud's phenomenon? Firstly, the patient should have a careful history taken and physical examination made with special attention

given to signs and symptoms of connective tissue disease, in particular scleroderma. In addition, a test for antinuclear antibodies should be done. When signs and symptoms indicate an underlying connective tissue disease or when a positive antinuclear antibody test is obtained, more studies should be performed to detect subclinical organ involvement. These studies may include pulmonary function tests, in particular the diffusing capacity for carbon monoxide, and scintigraphy of the oesophagus to detect oesophageal hypomotility. Which patients should be followed up? Besides the aforementioned group with signs and symptoms of connective tissue disease or a positive antinuclear antibody test, patients who develop Raynaud's phenomenon at an older age or who present with severe Raynaud's phenomenon may be selected for follow up as they are at risk for developing a connective tissue disease.

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- 1 Raynaud M. *Local asphyxia and symmetrical gangrene of the extremities*. London: The New Sydenham Society, 1888: 1-150. (Selected monographs. Translated by T Barlow.)
- 2 Maricq H R, Weinrich M C, Keil J E, et al. Prevalence of Raynaud's phenomenon in the general population. *J Chron Dis* 1986; **39**: 423-7.
- 3 Kallenberg C G M. Early detection of connective tissue disease in patients with Raynaud's phenomenon. *Rheum Dis Clin North Am* 1990; **16**: 11-30.
- 4 Kallenberg C G M, Wouda A A, Hoet M H, van Venrooij W J. Development of connective tissue disease in patients presenting with Raynaud's phenomenon: a six year follow up with emphasis on the predictive value of antinuclear antibodies as detected by immunoblotting. *Ann Rheum Dis* 1988; **47**: 634-41.

- 5 LeRoy E C, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; **15**: 202-5.
- 6 Gerbracht D D, Steen V D, Ziegler G L, Medsger T A, Rodnan G P. Evolution of primary Raynaud's phenomenon (Raynaud's disease) to connective tissue disease. *Arthritis Rheum* 1985; **28**: 87-92.
- 7 Fitzgerald O, Hess E V, O'Connor G, Spencer-Green G. Prospective study of the evolution of Raynaud's phenomenon. *Am J Med* 1988; **84**: 718-26.
- 8 Kallenberg C G M, Wouda A A, The T H. Systemic involvement and immunological findings in patients presenting with Raynaud's phenomenon. *Am J Med* 1980; **69**: 675-80.
- 9 Campbell P M, LeRoy E C. Raynaud phenomenon. *Semin Arthritis Rheum* 1986; **16**: 92-103.
- 10 Wouda A A. Raynaud's phenomenon. Photoelectric plethysmography of the fingers of persons with and without Raynaud's phenomenon during cooling and warming up. *Acta Med Scand* 1977; **201**: 519-23.
- 11 Kallenberg C G M, Pastoor G W, Wouda A A, The T H. Antinuclear antibodies in patients with Raynaud's phenomenon: clinical significance of centromere antibodies. *Ann Rheum Dis* 1982; **41**: 382-7.
- 12 Rothfield N, Whitaker D, Bordwell B, Weiner E, Senecal J L, Earnshaw W. Detection of anticentromere antibodies using cloned autoantigen CENP-B. *Arthritis Rheum* 1987; **30**: 1416-9.
- 13 Venrooij W J van, Stapel S O, Houben H, et al. Scl-86, a marker antigen for diffuse scleroderma. *J Clin Invest* 1985; **75**: 1053-60.
- 14 Houtman P M, Kallenberg C G M, Fidler V, Wouda A A. Diagnostic significance of nailfold capillary patterns in patients with Raynaud's phenomenon. *J Rheumatol* 1986; **13**: 556-63.
- 15 Maricq H R, Spencer-Green G, LeRoy E C. Skin capillary abnormalities as indicators of organ involvement in scleroderma (systemic sclerosis), Raynaud's phenomenon and dermatomyositis. *Am J Med* 1976; **61**: 862-70.
- 16 Maricq H R, LeRoy E C, D'Angelo W A, et al. Diagnostic potential of in-vivo capillary microscopy in scleroderma (systemic sclerosis) and related disorders. *Arthritis Rheum* 1980; **23**: 183-9.
- 17 Houtman P M, Kallenberg C G M, Wouda A A, The T H. Decreased nailfold capillary density in Raynaud's phenomenon: a reflection of immunologically mediated local and systemic vascular disease? *Ann Rheum Dis* 1985; **44**: 603-9.
- 18 Groen H, Wichers G, ter Borg E J, van der Mark Th M, Wouda A A, Kallenberg C G M. Pulmonary diffusing capacity disturbances are related to nailfold capillary changes in patients with Raynaud's phenomenon with and without an underlying connective tissue disease. *Am J Med* 1990; **89**: 34-41.
- 19 Maricq H R, Weinberger A B, LeRoy E C. Early detection of scleroderma-spectrum disorders by in vivo capillary microscopy. *J Rheumatol* 1982; **9**: 289-91.
- 20 Harper F E, Maricq H R, Turner R E, Lidman R W, LeRoy E C. A prospective study of Raynaud phenomenon and early connective tissue disease. *Am J Med* 1982; **72**: 883-9.