BIOMARKERS OF VASCULAR DISORDERS IN RAYNAUD PHENOMENON

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Abstract: *Raynaud's phenomenon (RP) is defined as an episodic response to cold or emotional stress that causes color change of extremities. RP is classified into primary and secondary form. The latter is associated with connective tissue diseases, especially systemic sclerosis. Due to the gradual onset of the disease, the patient usually comes to medical attention with advanced disease with internal organs damage. Moreover, biomarkers that will facilitate an early diagnosis are being explored. The results of the studies reveal an increased level of von Willebrand factor and tissue plasminogen activator in patients who developed systemic scleroderma later in life, even in the absence of specific antibodies and capillaroscopic changes. Also, in experimental models, extractable nuclear antigenes prove to have a direct profibrotic activity. Therefore, combination of biomarkers and capillaroscopy will allow a very early diagnosis and therapeutic management for a better outcome of patients with connective tissue disorders.*

INTRODUCTION

Raynaud's phenomenon is defined as an episodic response to cold or emotional stress that causes change in color of extremities and symptoms such as numbness, pain and tingling can be associated.(1)

Raynaud's phenomenon (former Raynaud syndrome/disease) is classified into primary and secondary form. Primary RP is caused by functional changes in vessels and is not associated with tissue loss. In contrast to primary RP, secondary RP occurs in the context of a systemic condition, most often in systemic scleroderma, mixed connective tissue disease, dermatomyositis, overlap syndromes and is characterized by important ischemia that can lead to digital ulcers or gangrene.

The pathogenesis of the vascular disease in secondary Raynaud phenomenon involves lots of different cells and pathways. A complex interaction between endothelial cells, immune cells, fibroblasts contribute to progression of angiopathy. The early activation of endothelial cells is probably the initiating event in disease pathogenesis.

The exact mechanism for the widespread vascular disease in secondary RP is still unknown, viral or bacterial infection, ischemia and environmental factors were suggested.

RP can be the only sign of impeding connective tissue disease (CTD) for many years. Thus, making a difference between primary and secondary Raynaud phenomenon is of a great importance, allowing early identification of risk group patients, who are prone to develop connective tissue disease. Current guidelines strongly suggest screening for antinuclear antibodies and nail fold capillaroscopy in any patient presenting with RP.(2)

Capillaroscopic changes were thought to be the earliest manifestation of microangiopathy due to local hypoxia, but recent studies show a marked increase in endothelial dysfunction markers in patients with RP who subsequently develop capillaroscopic changes and CTD.

Considering the fact, that scleroderma spectrum disorders usually have gradual onset and patients rarely come to physician before serious complication occur, an early diagnosis is crucial in order to prevent irreversible changes in target organs. Therefore, identification of early vascular dysfunction biomarkers is of a great value.

The involvement of vessels in secondary RP mainly targets microcirculation, with a focus on capillaries. According to the existing data, the activation of endothelial cells leads to an exaggerated expression of adhesion molecules, leading to inflammation, tissue hypoxia and fibrosis.

Gualtierotii et al. studied the relation between levels of endothelial markers in patients with RP and subsequent development of overt CTD in an observational prospective study that included 82 RP patients. The results of the study revealed an increased level of Il-6, von Willebrand factor and tissue plasminogen activator in patients who developed systemic scleroderma later in life, even in the absence of specific antibodies and capillaroscopic changes.(3)

Von Willebrand factor (VWF) is a large multimeric glycoprotein that has two critical functions in primary hemostasis: firstly, it acts as a bridge molecule at the sites of vascular injury for normal platelet adhesion, and under high shear conditions; secondly, it promotes platelet aggregation. VWF also plays an important part in fibrin formation.

Additional functions of VWF include roles in inflammation, such as leukocyte extravasation and recruitment to the endothelial cell surface and regulation of complement activation. It also plays roles in angiogenesis, angiodysplasia, cell proliferation, and apoptosis.(4,5)

Tissue plasminogen activator (tPA, tissue-type plasminogen activator) is a serine protease that can be found on

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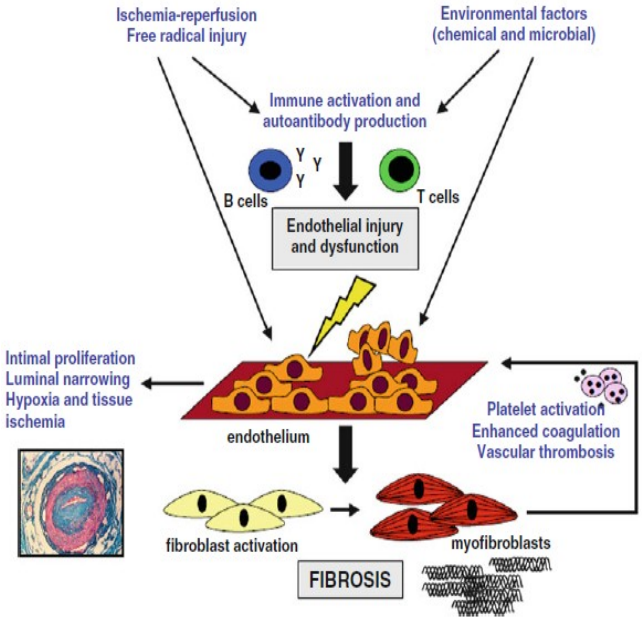
endothelial cells lining the blood vessels) involved in the breakdown of blood clots (fibrinolysis).

Interleukin-6 (IL-6) is a multifunctional cytokine that plays a central role in host defense due to its wide range of immune and hematopoietic activities and its potent ability to induce the acute phase response.(5-7)

Figure no. 1. Pathogenesis of vasculopathy in systemic sclerosis



Pro-inflammatory cytokine Il-6 is known to be involved in the pathogenesis of CTD, especially SSc. It was proved, that the level of this interleukin is markedly increased in serum and skin biopsy of patients with SSc.

The data from the study suggests that microangiopatic changes in capillaries of affected individuals happen in preclinical stage of the disease. Furthermore, predictive ability to discriminate patients with secondary RP from primary RP was very high for vWF and moderate-to-high for t-PA and IL-6.

Results that were obtained in the above-mentioned study were in agreement with data on early SSc.(8-10)

In scientific literature the relationship between capillaroscopic abnormalities and biomarkers of endothelial injury – endothelin-1, sE-selectin and high sensitive CRP was analyzed.

Endothelin-1, as well as e-selectin are specific for endothelial cells and are first to be released in case of endothelial dysfunction. These two substances are responsible for vasoconstriction and promotion of inflammatory process with consequent microvascular damage.(11)

The results of some studies showed an association of increased level of Endothelin-1 and presence of microangiopathy was highlighted.

Some authors stress the importance of extractable nuclear antigens in inducing fibrosis in cultured human fibroblasts, with the direct involvement of systemic scleroderma specific antibodies in pro-fibrotic process.

Therefore, this data could be used to advocate for the early use of immunosuppressive drugs at the pre-clinical stage of the disease for a better outcome.(12)

CONCLUSIONS

In conclusion, the existing data suggest that detection of endothelial injury early in the course of the disease can facilitate the management of RP and the detection of patients from the risk group before the capillaroscopic changes or antibodies are seen.

All of the above has the potential to change the existing criteria for SSc, switching to earlier signs of the disease, leading to a better outcome in patients with CTD.

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