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Raynaud's phenomenon — the clinical picture, treatment and diagnostics

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Abstract

Raynaud's phenomenon is the triphasic phenomenon which consists of sudden paling of distal parts of the body with the following cyanosis and occurance of erythema in the third stage. This phenomenon is a result of peripheral microcirculation disorder and usually appears after exposure to cold. If the RP is a primary, idiopathic (not associated with other diseases) then the other name for this condition is Raynaud's disease (80% of RP cases). If the RP is secondary to other medical conditions such as connective tissue disorders, arterial alterations etc., then Raynaud's syndrome is diagnosed and that is why further diagnostics is required in every case of RP.

Key words: Raynaud's phenomenon, capilaroscopy, connective tissue disease, scleroderma

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Introduction

Raynaud's phenomenon (RP) is a disorder of microcirculation where a recurrent, reversible vasospasm of distal small vessels is observed. This phenomenon mainly affects such vessels as small arteries (arterioles), precapillary vessels, as well as postcapillary vessels [1]. It was first described by Maurice Raynaud in the 19th century. Among his patients, the French doctor observed a distinct triphasic vascular reaction of distal parts of the body [2].

Clinically, two types of RP can be distinguished — primary RP (of a relatively benign course) and secondary RP, which occurs secondarily to other medical conditions such as connective tissue disorders [3, 4]. Primary RP, if idiopathic and not associated with other diseases, it is referred to as Raynaud's disease (80% of RP cases). If the RP is secondary to other medical conditions such as connective tissue disorders, arterial alterations etc., Raynaud's syndrome is diagnosed [5, 6].

Risk factors

The most common risk factor that can lead to RP is exposure to cold or a sudden change in temperature (for example entering an air-conditioned room) [3]. Moreover, factors such as emotional stress, exposure to vibrations, excessive activities requiring precise movements of the fingers, smoking [7], as well as therapy with beta-blockers may also provoke the paroxysmal vasospasm of small vessels [3, 8].

Raynaud's disease — primary Raynaud's phenomenon

Raynaud's disease is a relatively rare phenomenon, affecting 5–10% of the population worldwide. The incidence may vary depending on the patient's gender (1% of men, 20% of women) or climate [3]. It is a vasomotor disorder of small vessels of acral parts of the body, where a sudden pallor is observed. This symptom is symmetrical, however, it may present with varying severity in different locations [9]. This phenomenon is diagnosed earlier and more frequently in young women (15–30 years old) especially with low blood pressure [4, 9] (Fig. 1). The aberration of blood flow caused by the sudden vasospasm of small vessels is not severe enough to cause necrosis or other trophic lesions due to limited blood supply. As Raynaud's disease is only

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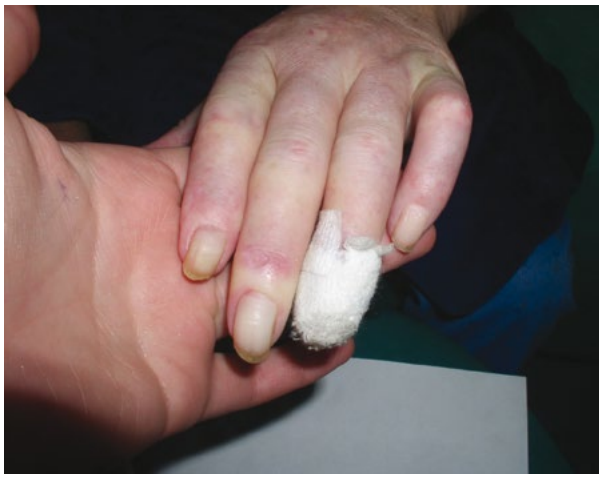

Figure 1. Raynaud's phenomenon of distal phalanges

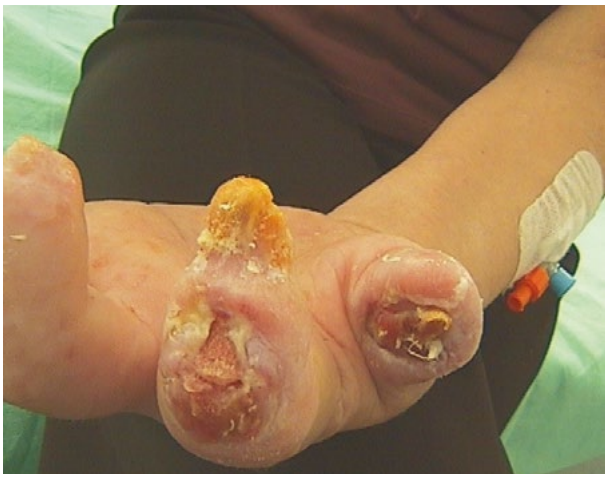

Figure 2. Autoamputation of distal phalanges

a functional disorder, no structural changes of the vessel wall are present. Comparing with the secondary Raynaud's syndrome, the vasospasm in Raynaud's disease is relatively rare, less severe and patients usually lack anti-nuclear antibodies ANA (or the ANA titer may be very low).

Raynaud's syndrome — the secondary Raynaud's phenomenon

Secondary Raynaud's phenomenon, in contrast to the primary one, is not an isolated symptom, but an integral part of a spectrum of different symptoms of chronic connective tissue diseases. Disorders, most often heralded by RP are: systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), dermatomyositis (DM), Sjögren syndrome (SS) and rheumatic arthritis [9].

The vasospasm of small vessels in this syndrome is more frequent, asymmetric, very painful and strong enough to cause trophic lesions in distal parts of the body due to the lack of sufficient oxygenation of the tissues [5]. Patients very often suffer from small erosions, ulcers and even necrosis of the fingers in rare cases [3, 9, 10]. Hypoxia is also a main cause of bone resorption and autoamputation of distal phalanges in patients diagnosed with SSc (Fig. 2). In secondary RP, osteolytic changes most frequently affect the first digit of the hand and laboratory results show high titers of ANA and erythrocyte sedimentation rate. Histopathological examination in Raynaud's syndrome, in contrast to Raynaud's disease, shows alterations of the vessel wall.

The first symptoms of Raynaud's syndrome start at the age of 30 in young adults, in 20–30% of cases about 20 years before any other symptoms of the underlying connective tissue disease, which is why further diagnostics of this disorder are essential for the patient [6].

The shorter the period between the first paroxysmal vasospasms in the fingers and other signs of the primary illness, the more severe this illness is. A proper, early evaluation and diagnosis of the underlying disease enables physicians to choose the right treatment. Such measures may limit or even delay the formation of irreversible vascular lesions, which in advanced cases can even be the cause of critical ischemia of the phalanges [11]. Raynaud's phenomenon may also be diagnosed in thromboangitis obliterans, also known as Buerger's disease, as well as in a wide range of vasculitis syndromes, where the primary process is the inflammation of the vessel wall (small, medium and large vessels) [12].

Pathogenesis of Raynaud's phenomenon

Pathophysiology of the whole process is sophisticated and not well established. However, it is indubitable that the RP results from the imbalance of intravascular chemical factors (a predominance of vasoconstrictive factors) and anatomic issues (affecting only small vessels). Decreased production of nitric oxide (NO) with increased levels of endothelin-1 profoundly limits the vasodilatation, triggering excessive vasoconstriction [13]. Due to the elevated levels of profibrotic factors such as endothelin-1 and angiotensin, the innermost layer of the vessel walls (tunica intima) becomes thicker, which additionally limits vasomotor activity. It has been documented, that the frequency of sudden vasospasms is higher in the pre-ovulation period and during estrogen therapy, which proves the distinct influence of estrogens on the pathogenesis of this process [1, 14].

Clinical picture

Regardless of the etiology of Raynaud's phenomenon, the basic feature of this process is its triphasic

character [4]. Paroxysmal vasospasm profoundly limits the tissue's blood supply, causing sudden pallor of the fingers (the ischemic phase), followed by the hypoxic phase, where affected fingers become cyanosed, whereas the last, third phase is based on vasodilatation and consecutive reperfusion [5]. Patients often complain about accompanying symptoms such as paresthesia, numbness, swelling and a tingling in the affected fingers [8, 15, 16]. The clinical picture of Raynaud's phenomenon may vary from mild and rare paroxysmal pallor of single fingers to severe symptoms which strongly influence the patients' quality of life [1]. Raynaud's phenomenon most frequently affects fingers and toes, but it may also be observed in other acral parts of the body such as auricles, the nose, nipples or the tongue [3, 7, 17]. Classic RP vasospasm lasts for 20 minutes on average, but in some cases it may even take a few hours [4]. Further diagnostics of RP are advised, when it takes more than 20 minutes for the affected tissues to recover physiological temperature after exposure to cold. The gold standard for diagnostics is the capillaroscopy of the nail bed.

Diagnostics — capillaroscopy

This non-invasive method uses a magnifying technique in order to evaluate the morphology of the capillaries of the nail bed, where the vessels are most visible owing to their parallel course against the skin surface. The video dermatoscope is the most frequently used device when conducting this examination.

A properly conducted video dermatoscopy requires the following conditions: an ambient temperature of 20–22 degrees Celsius; adaptation time (15–20 minutes); psychical comfort; usage of immersion or other oily substance (for visual improvement) and choice of examination site (the nail bed of fingers II–V or III–V).

During the examination, the following elements are evaluated:

— epidermal translucency,
— vessel morphology, quantity and composition,
— presence of oedema or haemorrhages,
— blood flow through vessel loops,
— visibility of venous subpapillar plexus.

Capillaroscopy is a basic examination used to distinguish primary and secondary Raynaud's phenomenon. The first one presents with no alterations of the vessel wall, in contrast to Raynaud syndrome.

Vascular structural changes are mainly observed in SSc (scleroderma pattern) as well as in other connective tissue diseases [18].

A proper capillaroscopic pattern is characterized by the presence of 9 to 14 regular distributed, hair pin shaped capillaries per 1 mm (Fig. 3). In SSc a distinct scleroderma pattern is described. There are three stages: early, active and late. The early stage is characterized by a few enlarged/gigantic vessels (loops), haemorrhages, and regular distribution of the vessels.

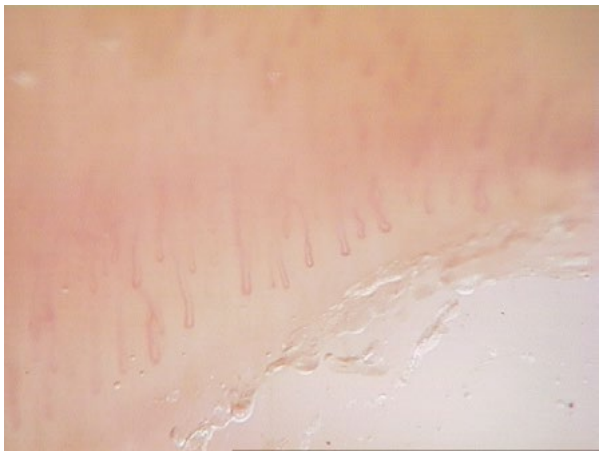

Figure 3. Normal capillaroscopy

Figure 4. Irregular capillaries of the nail bed

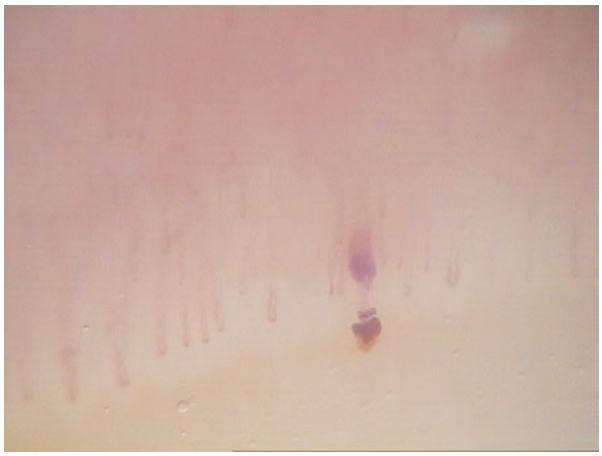

Figure 5. Petechiae in Raynaud's phenomenon

The active phase presents with enlarged/gigantic vessels, haemorrhage, a slight disorder in distribution and only a small number or lack of branched capillaries (Fig. 4).

The late phase presents an irregular enlargement of loops, a few or a lack of hemorrhages (Fig. 5), severe

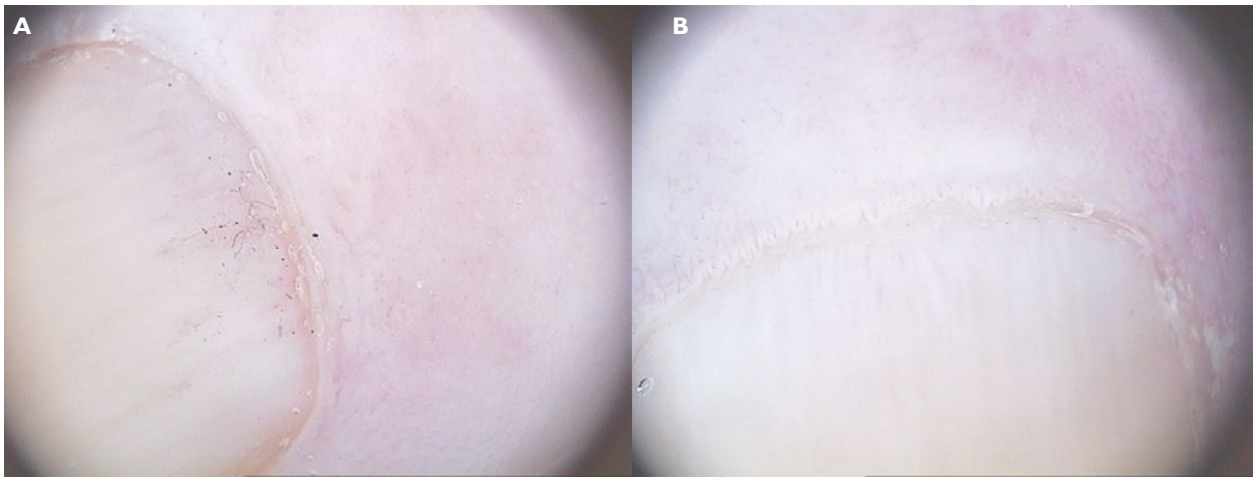

Figure 6. Late phase of Raynaud's phenomenon

capillary atrophy of the avascular regions and multiple branched capillaries (Fig. 6). Some of the mentioned signs are observed in other connective tissue diseases and then described as a scleroderma-like pattern [18].

A capillaroscopy is an important and reliable tool in the diagnostics of connective tissue disorders and has been involved in EULAR and ACR criteria. This test seems to be a very effective measure due to the fact that it is relatively simple, inexpensive and has a high diagnostic value (up to 87% of patients with SSc have vascular lesions in the early stage of the disease).

Treatment

The aim of the therapy is to take countermeasures against the vasoconstriction and its effects. The treatment is based on non-pharmacological and pharmacological means. The first line of the treatment is based on avoiding triggering factors such as exposure to cold, sudden changes of temperature, stress and smoking. Moreover, during the vasospasm, it is advised that one should place one's hands under warm running water or to rub one hand against the other to intensify blood flow [1].

Medication is available to treat more severe forms of the condition, with systemic or topical therapy. The first group of drugs comprises calcium channel blockers such as nifedipine or diltiazem, which are highly effective in severe cases of RP. Concomitant therapy with a calcium channel blocker and a selective beta blocker has very promising results compared to monotherapy with a calcium channel blocker ($p < 0.001$) [19]. Phosphodiesterase 5 selective inhibitors such as sildenafil, tadalafil, vardenafil are also widely used for vasomotor disorders due to their vasodilative effects [20]. Selective serotonin re-uptake inhibitors have also been shown to have a positive influence on Raynaud's phenomenon, however, these drugs are not frequently prescribed [20].

Synthetic prostacyclin analogs administered intravenously (eg. alprostadil, iloprost) are further useful pharmacological agents. These prostacyclin analogs have a strong vasodilative effect, which considerably improves the clinical condition, especially among patients with ulcers and erosions. Bosentan, which is the endothelin receptor antagonist (ET1-R) has also been proven to prevent the formation of new ulcers. The effectiveness of certain endothelin receptor antagonists (ET1-R) is now being evaluated (ambrisentan) [19]. Vasodilatative drugs such as angiotensin-converting-enzyme inhibitors (captopril, enalapril), moxisylyte, buflomedil, beraprost and dazoxiben did not demonstrate any positive therapeutical effects on this condition [20].

Among the topical drugs, nitroglycerine is the most effective and most widely used, due to its positive impact on the severity of vasospasms, as well as their frequency. However, the use of nitroglycerine is limited due to adverse effects such as headaches, nausea, hypotension and vertigo. New trials are being conducted on a new generation of nitroglycerine derivatives, which do not have side effects. Surgical treatment or injections of botulinum toxin, resulting in a reduction of sympathetic nervous system function, are rarely performed nowadays.

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