



International Journal of Surgery Science

E-ISSN: 2616-3470

P-ISSN: 2616-3462

© Surgery Science

www.surgeryscience.com

2019; 3(4): 148-150

Received: 13-08-2019

Accepted: 15-09-2019

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Raynaud's phenomenon

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DOI: <https://doi.org/10.33545/surgery.2019.v3.i4c.233>

Abstract

Raynaud's phenomenon is a peculiar vascular sign. It may be primary which is best described as Raynaud's disease or secondary. Secondary Raynaud's phenomenon is due to connective tissue disorders or occupational in origin. Identifying the type is essential for treatment. Associated clinical features and laboratory tests help in making the distinction. The paper discusses the essential practice points related to the phenomenon.

Keywords: Raynaud's phenomenon diagnosis management

Introduction

Raynaud's phenomenon is a commonly encountered clinical feature affecting the fingers and toes. The phenomenon is named after Morris Raynaud who defined the first case in 1862 as episodic, symmetric, acral vasospasm characterized by pallor, cyanosis, and suffusion [1, 2]. It may be primary or secondary to underlying disease. Primary type is described as Raynaud's disease whereas, the secondary type is usually associated with underlying systemic diseases, especially connective tissue disorders [3]. Identifying the type is very important as the therapeutic approach is altogether different in the two types.

Clinical definition

Raynaud's phenomenon is best described as reversible spasm of the peripheral arterioles in response to cold or stress. Raynaud's phenomenon is usually best seen in the distal digits but could also involve the nose, ears and tongue [3]. A typical episode has three responses:

- Phase 1: Pallor due to severe vasoconstriction of the precapillary muscular arterioles
- Phase 2: Cyanosis due to pooling of deoxygenated venous blood
- Phase 3: Erythema due to reactive increase in the blood supply

Pathophysiology

Primary Raynaud's phenomenon is related to functional alterations alone, whereas, in contrast secondary Raynaud's phenomenon reflects a variety of structural microvascular abnormalities. [4, 5] The underlying mechanism of Raynaud's phenomenon can best be discussed under three categories - vascular, neural and intravascular abnormalities.

Vascular abnormalities

Deficiency of vasodilatory mediators especially nitric oxide may be the primary cause [5, 6]. In addition, vasoconstrictor agents such as endothelin-1 are found to be in high levels in patients with secondary Raynaud's phenomenon. Release of endothelin-1 is triggered by vasoactive stimuli, angiotensin, vasopressin and β -transforming growth factor [7]. In patients with collagen vascular disorder, structural abnormalities related to fibrotic proliferation of the vasculature have been found which is absent in primary Raynaud's phenomenon [8].

Neural abnormalities

Impaired vasodilation is typically seen in Raynaud's phenomenon [9]. An important neuropeptide calcitonin gene related peptide is a potent vasodilator secreted by nerves that supply the blood vessels [10, 11]. A diminished number of calcitonin gene related peptide releasing neurons have been found in skin biopsies of patients with primary Raynaud's

phenomenon and systemic sclerosis [11, 12]. Enhanced vasoconstriction in Raynaud’s phenomenon may involve over activity of alpha 2c adrenoceptors. These adrenoceptors have been found to enable cold induced vasoconstriction of blood vessels. Enhanced contractile response to alpha 2c adrenergic agonist and cooling in patients with primary Raynaud’s phenomenon maybe linked to increase protein tyrosine kinase activity [13]. This provides evidence to the fact that protein tyrosine inhibition maybe beneficial in the treatment of Raynaud’s phenomenon [14]. Neuropeptide Y is a potent vasoconstrictor seen in patients suffering from Raynaud’s phenomenon secondary to systemic sclerosis.

Intravascular abnormalities

Raynaud’s phenomenon is associated with following intravascular abnormalities:

1. Increased platelet activation and aggregation is seen in primary Raynaud’s phenomenon and systemic sclerosis [15].
2. Increased production of platelet thromboxane A₂ which is again a potent vasoconstrictor.
3. Impaired fibrinolytic system seen in systemic sclerosis.
4. Oxidative stress by reactive oxygen species.

Etiology

The cause of primary Raynaud’s phenomenon is still unknown. Majority of cases have been attributed to autoimmune etiology with cytokeratin 10 as a candidate autoantigen [17].

Causes of secondary Raynaud’s phenomenon are manifold.

- Autoimmune - Systemic sclerosis, mixed connective tissue disorder, rheumatoid arthritis, Sjögren’s syndrome,

cryoglobulinemia.

- Drugs - Beta blockers, clonidine, interferons, cytotoxic drugs.
- Environmental agents and injuries – Frostbite, repetitive occupational stress
 - Hand arm vibration syndrome seen in rock drillers, grinders, jack hammers [16].
 - Hypothenar hammer syndrome – This is a condition wherein ulnar artery aneurysms are seen in patients using the ulnar border of the palm as a hammer and thereafter thrombosis of the ulnar artery leading to localized Raynaud’s phenomenon in the medial two fingers [16].
 - Neuropathy - Carpal tunnel syndrome
- Other systemic diseases - Hypothyroidism, cancer, cold agglutinin syndrome, POEMS syndrome (Polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes)

Clinical features

Primary Raynaud’s needs to be differentiated from secondary Raynaud’s phenomenon. (Table 1)

Diagnostic criteria for primary Raynaud’s phenomenon:

1. Attacks triggered by exposure to cold/stress
2. Symmetric involvement
3. Absence of necrosis
4. Absence of detectable underlying cause
5. Normal capillary findings
6. Normal laboratory findings for inflammation
7. Absence of antinuclear factors

Table 1: Differences between primary and secondary Raynaud’s phenomenon

	Primary Raynaud’s Phenomenon	Secondary Raynaud’s Phenomenon
1.	Exaggerated physiological response to cold or stress	Secondary to serious underlying disease
2.	No arterial abnormalities	Arterial abnormalities present
3.	Normal nail fold capillaries	Abnormal nail fold capillaries
4.	Symmetric attacks	Asymmetric intense painful attacks
5.	Tissue complications absent	Ischemic lesions are common
6.	Age of onset is around 14 years	Age of onset is >30 years
7.	Blood investigations are normal	Blood investigations are abnormal
8.	Features of connective tissue disorder absent	Features of connective tissue disorder present
9.	Increase frequency of migraine and Prinzmetal angina (vasospastic disorders)	There is no association with vasospastic disorders.

Diagnostic criteria for secondary Raynaud’s phenomenon

Secondary Raynaud’s phenomenon is commonly associated with autoimmune diseases hence clinical features suggestive of autoimmune disorders need to be identified [18-20].

Eg: Sclerodactyly, calcinosis, arthritis, digital ulcers, bone pain, malar erythema, and arthritis should be looked for.

Lab investigations

- Complete blood count
- ESR
- C reactive protein
- Urine analysis
- Antinuclear antibody
- C3, C4 complement levels

If the above tests are normal then following tests should be done

- Thyroid function tests
- Serum protein electrophoresis
- Test for cryoglobulins
- Anti-topoisomerase antibodies
- Anti-centromere antibodies

- Serum creatinine kinase
- Rheumatoid factor
- Hepatitis panel
- Cold agglutinins
- Anti-phospholipid antibodies
- X -Ray of hands for subcutaneous calcification in CREST syndrome.

Specific tests

- Digital perfusion to nail fold vasculature by capillaroscopy
- Doppler arterial ultrasound
- Look for thromboangiitis obliterans, thoracic outlet syndrome

Treatment

General Measures [20-22]

1. Avoidance of exposure to cold, vibrating tools and emotional stress.
2. Avoidance of inciting drugs.
3. Smoking to be stopped immediately, completely and permanently.
4. Calcium channel blockers - these cause arterial vasodilation.

- They also have antiplatelet effects and reduces oxidative stress. Eg. nifedipine, amlodipine, diltiazem
5. Sympatholytics - Prazosin
 6. Angiotensin 2 receptor antagonists - these cause vasodilation and block the effect of angiotensin 2. Eg. losartan
 7. SSRIs - Eg. Fluoxetine, which gives better results in patients with primary Raynaud's phenomenon
 8. Selective serotonin antagonists - Ketanserin
 9. Statins - improves endothelium cell dysfunction, decrease platelet aggregation, decreases vascular smooth cell proliferation
 10. Antioxidants- Vitamin E, probucol
 11. Treatment of infections - Avascular areas more prone to develop infections - hence appropriate antibiotics and dressings are required.
 12. Fish oil containing omega 3 fatty acids which are beneficial in reducing primary Raynaud's phenomenon. They reduce blood viscosity and act as a substrate for production of prostacyclins.

Critical limb ischemia

Critical ischemia is characterized by severe pain, downward posture of the hand and if not relieved may lead to ulceration and gangrene [22- 25].

Treatment

- Prostaglandins are the treatment of choice for such patients.
- Iloprost causes vasodilation and inhibition of platelet aggregation. The dose is 0.5 - 2 ng/kg/min IV infusion for 6-24 hours for 2 - 5 days.
- Synthetic analogues of PGI₂ causes systemic and pulmonary arterial dilatation. Eg. Epoprostenol 0.5 - 6ng/kg/min infusion for 1-3 days. Action - it has vasodilator properties, contributes to inhibition of platelet aggregation as well as inhibition of smooth muscle proliferation.

Conclusion

Raynaud's phenomenon is a complex sign of vascular disease. Differentiating between primary and secondary Raynaud's phenomenon is pivotal for further treatment. Laboratory tests will help in making the differentiation. Primary Raynaud's phenomenon or Raynaud's disease requires supportive care only whereas secondary Raynaud's requires aggressive treatment of the underlying cause.

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