Series Editor: Frank L. Urbano, MD

Raynaud's Phenomenon

Frank L. Urbano, MD

Raynaud's phenomenon is a disorder characterized by one or more fingers becoming blanched, cyanotic, and red (often in that order), upon an individual's exposure to cold stimuli or emotional stress.[1] These color changes are attributable to several factors; however, they mainly result from vasospasms of the digital arteries. The disorder occurs fairly commonly and can have a variety of other presentations, ranging from mild discomfort to severe pain in the affected fingers. It can eventually lead to ulcerations, tissue necrosis, and gangrene. This article reviews the history behind the first description of Raynaud's phenomenon and discusses classification of the disorder. The article also reviews issues relating to the disorder's pathogenesis, clinical features, diagnosis, and treatment.

RAYNAUD'S PHENOMENON

Characterized by pallor, cyanosis, and reddening of the fingers (and sometimes other areas of the body). The color changes of the skin are usually precipitated by cold stimuli or emotional stress.

HISTORICAL PERSPECTIVE

Maurice Raynaud (1834–1881) was a French physician who trained at the University of Paris. He received a doctoral degree in medicine in 1862 upon completing his thesis entitled "Local Asphyxia and Symmetrical Gangrene of the Extremities."[2] He went on to earn another doctoral degree in letters for historical research in medicine and was elected to the Academy of Medicine in 1879.

In his thesis, Raynaud described several patients who developed cyanosis and other discolorations of their fingers when the digits were exposed to cold. One patient was described as having cyanosis "at the [tips] of the fingers" followed by the development of "a vermilion red" discoloration, which occurred every time her hands were exposed to the cold. Another patient had a quite dramatic reaction, which he described as follows:

> So soon as she allows her hands to be exposed to a rather low temperature the fingers become pale, oedematous, half flexed; they are attacked with painful sensations, numbness, and torpor; shortly afterwards, they become blue, then black, in their whole extent.[2]

This patient, however, was suspected of having scleroderma by those who later reviewed Raynaud's thesis, because she died less than 2 years after the onset of these and other symptoms, including atrophy of the fingers and toes, loss of facial expression, discoloration of the skin, and feebleness.

Raynaud believed that the pathogenesis of the phenomenon was attributable to a local reflex that mediated the constriction of the digital blood vessels. He carried out studies, including a pathologic examination of the digital arteries and experiments involving the interruption of the cervical sympathetic chain, but found that he could not elicit the phenomenon or explain its occurrence in any way other than as a local, possibly neurally mediated reflex. Since that time, more detailed descriptions of potential mechanisms involved in the pathogenesis of Raynaud's phenomenon have been outlined and are discussed later in this article.

CLASSIFICATION

An instance of Raynaud's phenomenon has traditionally been classified as Raynaud's *disease* when it occurs as a primary disease of unknown cause and as Raynaud's *syndrome* when it occurs secondary to a connective tissue disease, such as scleroderma.[3] This

Dr. Urbano is in general internal medicine, Mount Laurel Primary Care Physicians, Mount Laurel, NJ.

method of classification has caused some confusion among physicians, which has led some authors to suggest a clearer way of distinguishing cases of Raynaud's phenomenon[4] by using the terms *primary Raynaud's phenomenon* (PRP) and *secondary Raynaud's phenomenon* (SRP). PRP is used to designate Raynaud's phenomenon that is primary or idiopathic in nature.[4] SRP—marked by the same pathophysiology, signs, and symptoms as PRP—is used to designate Raynaud's phenomenon resulting from some known underlying disease, medication, or event.[4]

Diseases associated with SRP are numerous and include scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and many other vasculitides.[4] Other more common conditions that have been associated with SRP include peripheral vascular disease, diabetes mellitus, and carpal tunnel syndrome. Also, certain medications, such as β-blockers and ergotamine, have been associated with SRP. Occupational exposure to hand-transmitted vibration, trauma, and certain chemicals may be related to SRP, as well; in one study, approximately 38% of cases of Raynaud's phenomenon in men were estimated to have arisen from exposure to hand-transmitted vibration.[5] However, this incidence was much lower in women.

PATHOGENESIS

The pathogenesis of Raynaud's phenomenon is not completely understood. However, it can potentially involve several mechanisms that could give rise to the vasospasms of the digital arteries.[6] One mechanism corresponds to the increased sympathetic nervous system activity observed in patients with Raynaud's phenomenon. This increased activity is probably due to an increased density of α-adrenergic receptors on peripheral blood vessels. This increased density can cause the digital blood vessels to be hyperreactive to sympathetic stimuli. The hyperreactivity could, in turn, lead to the vasospastic attacks in the patients. Also, patients with Raynaud's phenomenon have a central nervous system sympathetic baroreceptor reflex abnormality. This abnormality can cause exaggerated vasoconstriction of the digital blood vessels when the baroreceptors are activated.

Moreover, the vascular endothelium is thought to be involved in the pathogenesis of Raynaud's phenomenon[3,6]; patients exhibit both endothelial damage and dysfunction. The damage may be attributable to repeated vasospastic attacks causing ischemic reperfusion injury to the endothelium. This injury causes the release of free radicals and other products that damage the endothelium. Endothelial dysfunction results from a decrease in the vasodilatory chemical nitric oxide. The cause of this decrease is not known, but the effect is a failure of the endothelium to appropriately relax, which results in vasospasms.

Neurohormonal factors are also considered to be important in the pathogenesis of Raynaud's phenomenon. The vasoconstrictor, endothelin-1, is abnormally elevated in patients, and there is a decrease in the number of neurons containing calcitonin gene–related peptide (CGRP), a very potent vasodilator. Some recent research has focused on the latter of these compounds[7]: researchers have observed that there is a specific deficit of CGRP neurons in the digital skin of patients with the disorder. This deficit undoubtedly leads to vasospasms. CGRP neurons have been found in many organs, a fact that may explain the systemic effects observed in some patients with Raynaud's phenomenon.[3]

Hematologic abnormalities have also been observed in patients with Raynaud's phenomenon and may contribute to its pathogenesis. Abnormal platelet and leukocyte aggregation has been observed. Elevations of the levels of factor VIII–von Willebrand factor antigen and fibrinogen have also been observed, with the level of the former correlating to the severity of the vasospastic attacks.

CLINICAL AND LABORATORY CHARACTERISTICS

Classically, Raynaud's phenomenon is associated with 3 specific stages—the so-called triphasic color change—in response to an individual's exposure cold stimuli (or emotional stress).[3] Initially, pallor develops in the fingers; this is caused by vasospasm of the digital arteries and concomitant reduction in blood flow. Next, cyanosis develops; this is caused by pooling of deoxygenated blood and then flow of this deoxygenated blood through the digital blood vessels. Finally, there is reactive hyperemia and rubor (or reddening) of the fingers, resulting from the refilling of the vasospastic vessels with oxygenated blood. Approximately 60% of patients will exhibit all 3 color changes.[1] Some patients will exhibit only 1 (10%–30%) or 2 (14%–40%) of the color changes.

In addition to the digital color changes, patients report symptoms including numbness and a lingering feeling of coldness in the fingers during the early stages of the disorder's course. These symptoms make patients uncomfortable,[1] but they are usually not in pain at this time. However, as the course of the disorder progresses, patients may experience varying degrees of pain.

Other than the color changes of the fingers and the numbness and coldness patients may feel, physical examination results are normal in patients with Raynaud's

phenomenon during the early stages of the disorder's course. As the digital arteries become more constricted, other outward changes—including chronic paronychia, nail pitting, hair loss, scarring, fissures, and ulcerations of the fingers—become apparent. Patients with ulcerations of the fingers and eventual necrosis will be particularly symptomatic. Eventually, if the condition is not treated (or if treatment is not successful), dry gangrene can occur, resulting in the need for amputation.

Raynaud's phenomenon usually affects the fingers, but in up to 40% of patients, the toes may be affected as well.[8] The thumb is usually spared. More rarely, the tip of the nose, chin, earlobes, tongue, and nipples may be affected. The fact that Raynaud's affects other areas of the body suggests that it may actually be a systemic disorder. Patients with the disorder have been documented to have decreases in myocardial perfusion during cold challenge,[9] and there is a higher incidence of angina in patients with Raynaud's phenomenon. Decreases in perfusion in many other tissues—including those of the esophagus, kidney, lung, and placenta—have also been documented.[3] Furthermore, decreases in perfusion in the cranial arteries have been documented[3]: such decreases explain the higher incidence of migraines among patients with Raynaud's phenomenon.

In particular, proposed clinical and laboratory criteria for the identification of PRP include episodic attacks of acral pallor or cyanosis; no evidence of digital pitting, ulcerations, or gangrene; normal nail-fold capillarioscopy results; negative antinuclear antibody testing results; and a normal erythrocyte sedimentation rate.[4] These criteria are effective in excluding the majority of patients with underlying connective tissue diseases. Epidemiologically, most patients with PRP tend to be women, and the clinical course is usually mild, with only rare instances of tissue loss or necrosis.[1]

Clinical and laboratory criteria proposed for the identification of SRP include abnormal nail-fold capillarioscopy results; positive antinuclear antibody testing results; presence of digital pitting, ulcerations, or gangrene; and evidence of other organ system involvement, including gastrointestinal, cardiopulmonary, or renal abnormalities.[4] Patients with SRP usually have a much more complicated clinical course, with multiorgan system complications occurring frequently.

DIFFERENTIAL DIAGNOSIS

There are a number of disorders that may mimic Raynaud's phenomenon and that need to be considered in the differential diagnosis.[8] One such entity is cold digits, in which patients complain of lingering feelings of coldness and possibly pain in the fingers after exposure to cold stimuli. However, the fingers of the patients with this disorder do not go through the characteristic color changes associated with Raynaud's phenomenon. The cause of cold digits is not clear but may represent excessive sympathetic activity leading to reflex vasoconstriction.

Acrocyanosis is a disorder primarily affecting young women in which the digits turn blue whenever exposed to cold. The condition is not associated with pain or any of the other outward physical changes associated with Raynaud's phenomenon. Central cyanosis is a condition in which there is cyanosis of the mucous membranes and nail beds. Although this may at some point be confused with Raynaud's phenomenon, the presence of the mucosal cyanosis differentiates this condition from Raynaud's phenomenon.

Chilblains are rare forms of vasculitis that cause areas of the fingers to develop swellings, redness, and pain, as well as small ulcerations, upon exposure to cold. Although this may be difficult to differentiate from Raynaud's phenomenon, the ulcerations will usually heal spontaneously, in contrast to the ulcerations developing in relation to Raynaud's phenomenon. Some patients do go on to develop the color changes characteristic of Raynaud's phenomenon; however, the true relationship between these 2 conditions is not clear.

DIAGNOSIS

The diagnosis of Raynaud's phenomenon is primarily a clinical one, based on a history of color changes of the fingers.[8] Beyond the observance of any existing finger discolorations, a physical examination is rarely helpful. General laboratory testing by itself is usually not helpful, as well.[1]

Nail-fold capillarioscopy may be helpful in diagnosing Raynaud's phenomenon associated with connective tissue diseases.[1,3,10] When Raynaud's phenomenon is caused by such diseases, there may be enlarged, dilated, distorted, swollen, and irregularly spaced capillary loops. In addition, nail-fold capillaries may be absent in patients with an underlying connective tissue disease. When Raynaud's phenomenon is primary or idiopathic, results from nail-fold capillarioscopy are normal.

TREATMENT

Treatment of Raynaud's phenomenon is multifactorial.[10,11] If any causative disease is established, treatment for that condition should be provided. Once etiology (if any) has been established, nonpharmacologic treatment of the symptoms of Raynaud's phenomenon also

should be considered. Patients' avoidance of cold (eg, by wearing gloves or layered clothing), smoking, and vasoconstrictive drugs (including decongestants, caffeine, and amphetamines) is necessary. Education about methods to prevent attacks may be helpful. Various complementary techniques may also be helpful, including relaxation, biofeedback, behavioral training, acupuncture, and herbal medicines. The effectiveness of these methods is inconsistent, however, and they are therefore not routinely recommended.

Pharmacologic treatment for patients with Raynaud's phenomenon involves several classes of medications. Calcium-channel blockers are the most widely used agents, and nifedipine is the most thoroughly studied member of this class. Patients with Raynaud's phenomenon treated with nifedipine consistently show a significant reduction in both the frequency and severity of vasospastic episodes, with objective improvements in measurements of digital blood flow, as well.[11] The use of nifedipine is only limited by adverse effects, which can include headache, dizziness, flushing, and peripheral edema. Other calcium-channel blockers that have been found to be effective in the treatment of patients with Raynaud's phenomenon include amlodipine, isradipine, and felodipine. Calcium-channel blockers that have been shown to be inconsistent with regard to effectiveness include nicardipine and diltiazem.

Numerous other medications have also been used in the treatment of Raynaud's phenomenon. They include angiotensin-converting enzyme (ACE) inhibitors and angiotensin-blockers (eg, losartan). They also include α-adrenergic blocking agents (eg, guanethidine, phenoxybenzamine, and prazosin) and other vasodilators (eg, minoxidil and nitroglycerin). However, these drugs have limited utility and numerous unacceptable side effects.

More recently, iloprost, an intravenously administered prostacyclin analogue, has been shown to be quite useful in patients with resistant Raynaud's phenomenon and ischemic or infarcted digits.[3] The utility of this agent is limited, however, by its need to be administered intravenously.

Potential future therapies for Raynaud's phenomenon are abundant and include endothelin-receptor blocking agents, CGRP infusions, L-carnitine, L-arginine, and relaxin. Relaxin is a hormone with pharmacologic properties including vasodilation, inhibition of platelet aggregation, and stimulation of nitric oxide generation; it is currently being used in phase II clinical trials in patients with scleroderma skin disease and has shown favorable effects on the healing of digital ulcers.[3]

CONCLUSION

Raynaud's phenomenon is a relatively common disease with a presentation that varies from mild discomfort of the fingers to ulcers, necrosis, and gangrene. Its pathogenesis, however, is not fully understood. It is sometimes associated with underlying connective tissue diseases, and the nature of its course can vary from one that is benign to one that may threaten the viability of patients' tissues. Continued research should lead to newer and more effective agents to treat this sometimes debilitating disease. **HP**

REFERENCES

1. Browne BJ, Jotte RS, Rolnick M. Raynaud's phenomenon in the emergency department. J Emerg Med 1995;13: 369–78.
2. Maurice Raynaud (1834-1881). Raynaud's disease. JAMA 1967;200:985–6.
3. Ho M, Belch JJ. Raynaud's phenomenon: state of the art 1998. Scand J Rheumatol 1998;27:319–22.
4. LeRoy EC, Medsger TA Jr. Raynaud's phenomenon: a proposal for classification. Clin Exp Rheumatol 1992;10: 485–8.
5. Palmer KT, Griffin MJ, Syddall H, et al. Prevalence of Raynaud's phenomenon in Great Britain and its relation to hand transmitted vibration: a national postal survey. Occup Environ Med 2000;57:448–52.
6. Khan F. Vascular abnormalities in Raynaud's phenomenon. Scott Med J 1999;44:4–6.
7. Raynaud's phenomenon. Lancet 1995;346:283–90.
8. Coffman JD. Evaluation of the patient with Raynaud's phenomenon. Postgrad Med 1985;78:175–7, 180–3.
9. Belch JJ. The phenomenon, syndrome and disease of Maurice Raynaud. Br J Rheumatol 1990;29:162–5.
10. Ling SM, Wigley FM. Raynaud's phenomenon in older adults: diagnostic considerations and management. Drugs Aging 1999;15:183–95.
11. Sturgill MG, Seibold JR. Rational use of calcium-channel antagonists in Raynaud's phenomenon. Curr Opin Rheumatol 1998;10:584–8.