Raynaud’s & Scleroderma: Diagnosis and Treatment

Published by the Irish Raynaud’s & Scleroderma Society
January 2007
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Raynaud’s & Scleroderma Ireland is a registered charity offering practical aid and supportive counselling to sufferers from these two connected conditions. It provides advice on coping strategies for everyday living, information and support to both the newly diagnosed and the long-term patient, networking opportunities within Irish communities, and physical aids to ease patients’ lives. In addition, the Irish Raynaud’s & Scleroderma Society actively pursues its goals of increased awareness, education within the medical/nursing community, and research into causes and treatments.

Raynaud’s & Scleroderma Ireland wish to thank Professor Carol Black CBE for her assistance in the preparation of this booklet.
Raynaud’s and Scleroderma: the connection

Scleroderma is one of a number of chronic, disabling, and progressive Connective Tissue Diseases. In 90% of patients suffering from these diseases, notably Scleroderma, Lupus, and Mixed Connective Tissue Disease, Raynaud’s is present and is usually the first symptom. For this reason, patients presenting with Raynaud’s should be promptly assessed for Connective Tissue Disease, using blood tests, capillaroscopy, thermography, or other methods, as available.

Connective Tissue Diseases associated with Raynaud’s:

- Scleroderma (Systemic Sclerosis)
- Dermatomyositis
- Rheumatoid Arthritis
- Polymyositis
- Sjögren’s Syndrome
- Vasculitis
- Systemic Lupus Erythematosus (SLE)
- Anti-phospholipid Syndrome
- Undifferentiated Connective Tissue Diseases

Primary Raynaud’s: diagnosis

Raynaud’s is a common circulatory disorder, episodic in nature, and most often seen in women. Its hallmark is bi-phasic or tri-phasic colour change of the extremities as the capillaries contract abnormally. During a Raynaud’s attack, the digits, and less commonly the nose and ear-tips, turn white, blue, and red in an exaggerated response to exposure to even moderate cold or stress. This series of colour-changes is distinctly different from permanently cold, blue or white hands and feet. The Raynaud’s patient will usually complain of pain, numbness, or tingling, especially during the red phase. During the white phase, the digits are numb and lifeless, and normal activities must be suspended. Raynaud’s may also affect the internal organs, such as the stomach or the lungs.

The diagram below demonstrates a series of questions that will lead to a correct diagnosis of Raynaud’s.
Primary Raynaud’s: treatment
Raynaud’s may affect 10% of any population without geographical or racial bias. Approximately 90% of sufferers are female, and the condition usually occurs first during the teens or early twenties. It is generally benign, patients needing no treatment beyond advice on ways to maintain a constant body temperature. However, Raynaud’s may also be severe, causing significant disruption to the blood supply. This may result in the formation of ulcers on the extremities that prove highly resistant to healing. In the worst cases gangrene results, requiring amputation. Prompt recognition and treatment can do much to modify the condition and improve the quality of life for sufferers, and a variety of topical treatments and drug therapies are available that may cure persistent lesions.

Treatment regimes begin with aids to increase body temperature plus natural remedies and changes in lifestyle, before proceeding to pharmaceutical therapies. Surgery is no longer a popular option. A once-common surgical procedure, cervical sympathectomy, has been shown repeatedly to be of little or no benefit, although lumbar sympathectomies for the feet can sometimes produce good results and may be performed by injection rather than by surgery. Digital sympathectomy, while not a cure, is occasionally of use to relieve severe pain, heal finger ulcers, and reduce the severity of attacks.

It is important to recognise that a variety of drugs are now available and that if one proves ineffective, another may be tried. Individual responses vary considerably. The first drug of choice, Nifedipine, is often not tolerated by patients because of its side-effects. Some drugs such as Iloprost may be given intravenously in hospital. Listed below are the drug therapies most often used. Several options exist within each group, and may be tried in sequence, if necessary. A drug should be tried for at least two weeks, with a lapse of three days before beginning a course of a different drug. To avoid side-effects, a low dose should be taken initially, at night, building up steadily to the full dose.

Calcium Channel Blockers:
- Nifedipine retard (Adalat) 10mg 2xday, increasing to 20mg 2xday
- Nifedipine LA 30mg daily
- Amlodipine 5-10mg daily
- Diltiazem 60mg 3xday

Angiotensin Converting Enzyme Inhibitors:
Start at low dosage to prevent blood-pressure problems.
- Captopril 6.25mg test dose; then 12.5mg 2xday to max 25mg 2xday
- Enalapril 5mg starting dose; increase to 10-20mg daily
- Lisinopril 2.5mg starting dose; increase to 10-20mg daily
- Quinapril 5mg starting dose; increase to 20mg daily
Angiotensin II Receptor Antagonists:
- Losartan 25mg daily; increase to 50mg daily
- Valsartan 40mg daily; increase to 80mg daily

Serotonin Re-Uptake Antagonists:
- Fluoxetine 20-40mg daily. Note: this drug is also used to treat depression, but its use in Raynaud’s is to dilate peripheral blood vessels.
- Sertaline 50mg daily; increase to max 200mg (doses of 150mg or more should be used for a max of 8 weeks)
- Paroxetine 20mg daily; increase by 10mg per week to max of 40 mg daily

GTN patches:
- A 5mg patch, or dose of 0.2mg/hr initially, in acute cases; increase to 10mg patch (0.4mg/hr) if required. Patient must remove patch for 12 hrs each day to prevent nitrate tolerance build-up.

Anti-Oxidants:
Taking both these provides maximum effect in preventing damage to blood vessels.
- Vitamin E 100-400 international units (iu)
- Vitamin C 500-1000mg daily

Evening Primrose Oil and/or Fish Oils:
These products are used to increase prostacyclin. Many proprietary brands are available. The gamolenic acid (GLA) content recommended is 320mg daily, so dosage of individual brands should reflect this. Other options are:
- Generic GLA 320mg daily (may be prescribed)
- OMACOR 2000-4000mg daily (may be prescribed)
- Maxepa concentrated fish oils 5 capsules 2xday
- Epogam 4x40mg capsules 2xday

Vasodilators:
These are given intravenously on an in-patient basis over 5 days. Treatment may be repeated a limited number of times.
- Iloprost (a nebulised version is also available and an oral version is on trial)
- Calcitonin Gene-Related Peptide
Secondary Raynaud’s: diagnosis

Some 10% of Raynaud’s patients suffer from underlying diseases, the most serious of which are the Connective Tissue Diseases.

Other possible causes to consider are:

- Malignancy
- Hypothyroidism
- Anorexia Nervosa
- Reflex Sympathetic Dystrophy
- Fibromyalgia
- Arterial Trauma

Occlusive Arterial Disorders:
- Carpal Tunnel Syndrome
- Thoracic Outlet Syndrome
- Thrombosis
- Thromboangitis Obliterans
- Embolisation
- Buerger’s Disease

Intravascular Disorders:
- Polycythaemia Vera
- Leukaemia
- Thrombocytosis
- Cold Agglutinin Disease
- Monoclonal Gammopathies

Chemical/Drug Reactions:
- β-Blockers
- Ergotamines
- Oral Contraceptives
- Bleomycin
- Vinblastine
- Cisplatin
- Vinyl Chloride

Occupational Disorders:
- Vibrating Machinery
- Cold Weather Hazards
The checklist below offers assistance in the diagnosis of underlying disease in patients who present with Raynaud's.

### CHECKLIST FOR CLINICAL ASSESSMENT

- Arthralgia/Arthritis
- Myalgia
- Skin rashes
- Bruising
- Absent pulses
- Changes in skin texture
- Photosensitivity
- Finger ulcers
- Oral ulceration
- Respiratory/Cardiac problems
- Depression
- Fever
- Alopecia
- Cerebral symptoms
- Increased blood pressure
- Oesophageal symptoms
- Dry eyes/mouth
- Muscle weakness
- Weight loss
- Weight gain
- Lymphadenopathy
- Vascular events, e.g. MI, early stroke
- Recurrent unexplained miscarriage

### Secondary Raynaud's: tests for Connective Tissue Disease

To test Raynaud's patients for the presence of Connective Tissue Disease, the two most important predictive methods are:

- Blood Tests for Anti-Nuclear Antibodies (ANAs). The results of these autoimmune serology tests must be interpreted within the clinical context, as some 5% of positive results will be clinically irrelevant.

- Capillaroscopy of the nailfold. This may be done (with experience) in the surgery using an ophthalmoscope, or by a Rheumatologist using a Nailbed Capillaroscopy System. Abnormal patterns include missing or destroyed capillaries, and large loops of damaged capillaries.

If both tests are negative, the patient is highly unlikely to develop a connective tissue disease and may be treated for Primary Raynaud's.

If the ANA is positive, yet the antibody is not associated with a particular disease, the patient should be reviewed regularly.

If the ANA is positive and disease-specific, the patient should be considered highly likely to develop that disease.

If the capillary pattern is abnormal, the patient should be considered at increased risk of developing connective tissue disease, and reviewed on a regular basis.
### Anti Nuclear Antibodies Specific to Diseases.

**Interpretation Dependent upon Clinical Correlation.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibody</th>
<th>Frequency</th>
<th>Clinical Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleroderma</td>
<td>Anticentromere</td>
<td>40%</td>
<td>Limited cutaneous disease; Micro/macro vascular disease;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Telangiectasia</td>
</tr>
<tr>
<td></td>
<td>Anti-topoisomerase-1</td>
<td>25%</td>
<td>Diffuse cutaneous disease; Interstitial lung disease, both</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>subsets</td>
</tr>
<tr>
<td></td>
<td>Anti-RNA-polymerases</td>
<td>20%</td>
<td>Diffuse cutaneous disease; Renal disease</td>
</tr>
<tr>
<td></td>
<td>Anti-U3RNP</td>
<td>5%</td>
<td>Diffuse cutaneous disease; Pulmonary Hypertension</td>
</tr>
<tr>
<td></td>
<td>Anti-PM-Sci</td>
<td>5%</td>
<td>Scleroderma/Polymyositis overlap</td>
</tr>
<tr>
<td>SLE</td>
<td>Anti-nDNA</td>
<td>70%</td>
<td>Lupus Nephritis</td>
</tr>
<tr>
<td></td>
<td>Anti-Sm</td>
<td>10-25%</td>
<td>Vasculitis; CNS Lupus</td>
</tr>
<tr>
<td></td>
<td>Anti-U1RNP</td>
<td>30%</td>
<td>Raynaud’s; Arthritis; Myositis; Mixed Connective Tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disease</td>
</tr>
<tr>
<td></td>
<td>Anti-Ro</td>
<td>40%</td>
<td>Photosensitive rash; SCLE; Neonatal Lupus; CHB; Sjögren’s</td>
</tr>
<tr>
<td></td>
<td>Anti-La</td>
<td>15%</td>
<td>As for Anti-Ro</td>
</tr>
<tr>
<td></td>
<td>Anti-rRNP</td>
<td>15%</td>
<td>CNS Lupus (psychosis, depression)</td>
</tr>
<tr>
<td>Sjögrens</td>
<td>Anti-Ro</td>
<td>60-90%</td>
<td>Extra-glandular disease; Vasculitis; Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Anti-La</td>
<td>35-85%</td>
<td>As for Anti-Ro</td>
</tr>
<tr>
<td>Dermato/Polymyositis</td>
<td>Anti-Jo01</td>
<td>30%</td>
<td>Antisynthetase syndrome</td>
</tr>
<tr>
<td></td>
<td>Anti-Mi2</td>
<td>10%</td>
<td>Dermatomyositis</td>
</tr>
</tbody>
</table>
Scleroderma (Systemic Sclerosis or SSc)

Currently estimated to occur in 2% of Raynaud’s patients, Scleroderma is the most deadly of the Connective Tissue Diseases. Once considered to be relentlessly progressive, it is now known to go into periodic remission if treated promptly, and even, occasionally, to go into remission spontaneously. However in the majority of cases Scleroderma progresses at varying and unpredictable rates, and will usually be the cause of death. Management can be maximized and prognosis improved by early diagnosis and referral to a rheumatologist, as treatments are available that arrest disease processes both in the internal organs and in the skin.

Scleroderma: diagnosis

A chronic disease of the immune system, connective tissue, and blood vessels, Scleroderma may be localised or systemic, and due to the enormous variety of its symptoms and its differing rates of progress, it is difficult to diagnose. Raynaud’s may precede other symptoms by some years.

In both the localised and systemic forms of Scleroderma, the skin becomes stiff, tight, and shiny as, in response to overactivity in the immune system, excess collagen builds up in the connective tissue, often on the hands and feet, making the skin inflexible and joints rigid. This is most often, but not always, the next recognizable symptom. There is no fixed pattern to the symptoms of Scleroderma, which are caused by the connective tissue thickening both externally and internally, and becoming fibrotic and inflexible. How disabling the disease is depends on where and how fast this is taking place. Generally, Systemic Scleroderma escalates by progressing to the major organs, hardening and shrinking the connective tissue to reduce organ function until the organ fails. About 10% of Scleroderma patients will develop Pulmonary Hypertension.

Early symptoms following onset of Raynaud’s may include:

- Tight shiny skin on hands and feet
- Dryness of the mouth/eyes due to lack of saliva/tears
- Difficulty in swallowing
- Bloating
- Reflux and throat ulceration
- Generalised weakness
- Fatigue
- Aching muscles
- Painful joints with arthritis or tendon friction
- Poorly functioning bowels

More serious symptoms indicate the development of Scleroderma in the lungs, heart, kidneys, gut, or other organs. It is important to subset Scleroderma, because subsetting and staging have prognostic and therapeutic implications.
The Two Types of Scleroderma

LOCALISED SCLERODERMA
Localised Scleroderma is most often seen in children and is classified into two types, occasionally combined. Early referral is critical because childhood disease, while self-limiting, can be associated with growth defects:

- **Morphea** develops as one or many slowly enlarging patches or plaques. These are usually oval in shape but vary in size and colour, and may enlarge or shrink, sometimes disappearing spontaneously.

- **Linear Morphea** can affect the growth of a limb, and afflicted children should be under specialist care. Beginning as a band of thickening skin, usually limited to one area of an arm or leg, it progresses to layers of tissue below the skin, affecting muscles and bones, the mobility of the underlying joints, and the growth rate of the limb. Drug therapy and physiotherapy have proved successful in retarding its progress, if diagnosed early, and it may go into remission spontaneously, although its effects are irreversible and it may reoccur. One form, En Coup de Sabre, creates a slash across the scalp and face that is particularly disfiguring.

Although it is rarely life-threatening, the morbidity problems of Localised Scleroderma may pose additional psychological stresses for both patients and family members. Children and, in particular, adolescents, may feel isolated and excluded from regular activities, resulting in depression. Particular care should be taken in the explanation of the disease process, treatment, and prognosis, and counselling may be beneficial.

SYSTEMIC SCLERODERMA
Scleroderma that spreads throughout the body is classified into two types depending on which parts of the body are involved. Both types of patients need to be under specialist care and should be referred as quickly as possible, especially if the skin is changing rapidly.

- **Limited Scleroderma** was in the past called CREST, because the pattern of involvement is usually limited to five symptoms that spell out these letters (Calcinosis, Raynaud’s, Esophageal Dysfunction, Sclerodactyly, Telangiectasis). Skin involvement is limited to the hands, face, feet, forearms, and lower legs. Although it is generally more benign than the diffuse disease, it is now known that Pulmonary Hypertension is more common in patients with Limited Scleroderma than in those with Diffuse Scleroderma. ACA antibodies are present in 70-80% of patients.

- **Diffuse Scleroderma** can be found at many different sites on the body, where scarred tissue and compromised circulation damage skin, joints, muscles, organs, intestines and other parts in no specific order. Diagnostic are the onset of skin changes within a year of Raynaud’s onset; tendon friction rubs, arthritis and myalgia; significant early incidence of interstitial lung disease, oliguric renal failure, myocardial involvement, and diffuse gastrointestinal disease. There is a high risk of renal failure. Scl-70 antibodies are present in 30% of patients.
**Scleroderma: treatment**

A Scleroderma patient needs to be under the care of a specialist team led by a rheumatologist. The GP, however, may be responsible for palliative care of individual symptoms early in the disease, such as treatment of digital ulcers and prescription of products to alleviate dry eyes, swallowing problems, and bowel disfunctions.

- For lack of lacrimation, Tears Naturale, Liquifilm, and Artelac are available in Ireland.
- To improve motility in the gut, the organ most commonly involved in Scleroderma, Domperidone (Motilium) may be tried. For Sjögren’s patients, however, a low-fibre diet should be followed.
- For acid reflux, and ulceration and scarring of the oesophagus, the proton pump inhibitors, Omeprazole (Losec) and Lansoprazole (Zoton) are effective.
- A variety of antacids including Gaviscon, Magnesium Trisilicate, and Aludrox may be tried, but not in combination with other drugs as they inhibit absorption.
- An out-patient throat-widening procedure is effective to improve swallowing.
- Physiotherapy has proved highly beneficial to keep the joints moving and increase blood circulation. Sufferers should be encouraged to do regular stretching exercises to prevent skin tightening around the joints.
- Unperfumed moisturising creams such as Aqueous Cream BP should be massaged into affected skin areas regularly. Children with Localised Scleroderma should receive steroid therapy under the care of a dermatologist or rheumatologist.

Targeted therapies will be prescribed by the specialist team for individual organs involved, and treatment will include attention to vascular damage.

Current disease-modifying therapies include Cyclophosphamide, Azathioprine, Methotrexate, low dose Prednisolone, anti-TGF beta therapy, and bone-marrow transplantation. Some of these treatments are still in the trial stage. Iloprost infusions improve blood supply and repair the endothelium, so helping heal ulcers. An oral form of this drug is currently on trial. Bosentan (Tracleer) has proved very effective in the treatment of PAH, and is currently on trial for control of other symptoms.

For education and emotional support, The Irish Raynaud’s & Scleroderma Society is a good source of help for patients. The Society operates several lines of assistance and is always available to reassure and give information and support to sufferers and their families. It is also a source of heating aids and natural therapies, and can provide networking opportunities with other patients, as well as equipment when this is not supplied by the Health Board. Patients should ring (01) 2020184 for assistance.
## MANAGEMENT OF RAYNAUD'S

### Simple, short attacks
- Get heating appliances & aids
- Wear thermal clothing
- Stop smoking
- Stop taking $\beta$-blockers
- Take natural remedies, e.g. gingko, ginger
- Attend to all sores & scratches promptly
- Avoid using chemicals & wear rubber gloves with cotton liners
- Modify activities to exclude cold water/weather/draughts

### Frequent, prolonged attacks, often accompanied by digital infarcts
- Start drug therapies, orally or by infusion
- Possibly, perform selective surgeries
- Test blood for Connective Tissue Disease
- Test by Nailbed Capillaroscopy System

### Secondary infection of digits
- Prescribe antibiotics
- Perform debridement
- Enlist Public Health Nurse for ulcer care

### Gangrene
- Prescribe Prostacyclins
- Encourage auto-amputation
- Perform sympathectomies