# Red Face and Its Relationship to Rosacea

Written by Maria Vinall

Rosacea, a chronic inflammatory skin disease of unknown etiology, occurs mainly in red-haired, blue-eyed, fair-skinned individuals of Northern European and Celtic origin. Frank C. Powell, MD, University College Dublin, Dublin, Ireland, discussed the association of rosacea with the Irish population, 87% of whom have skin types 1 or 2 (pale-to-fair white).

The National Rosacea Society Expert Committee on the Classification and Staging of Rosacea defines 4 (sometimes overlapping) subtypes: erythematotelangiectatic rosacea (ETR; seen as flushing or persistent facial redness), papulopustular rosacea (PPR; characterized by bumps, pimples, and/or raised red plaques in addition to persistent redness), phymatous rosacea (an often stigmatizing subtype in which the nose is enlarged), and ocular rosacea (swollen, watery, or bloodshot eyes accompanied by irritation, burning, or stinging) [Wilkin J et al. *J Am Acad Dermatol.* 2002].

Recent molecular (gene array) and cellular findings of the different subtypes noted a differential regulation of genes with certain genes overlapping, suggesting a developmental progression from one subtype to another [Steinhoff M et al. *J Investig Dermatol Symp Proc.* 2011]. A rosacea gene has not been identified, however.

A 2010 study estimated the prevalence of PPR among Irish subjects to be about 2.7% [McAleer MA et al. *J Am Acad Dermatol.* 2010]. No association was noted with ultraviolet exposure, cutaneous photodamage, actinic keratoses, or cutaneous malignancy. This differs from ETR, which is significantly associated with photodamage (occurs in about 16.3% of Irish individuals with higher levels of sunlight exposure compared with 6.8% with lower levels; $P < .0001$). It has been suggested that ETR and PPR may be different conditions rather than subtypes of the same disorder.

Peer-Reviewed Highlights From the

**23rd European Academy of Dermatology and Venereology Congress**

October 8–12, 2014
Amsterdam, The Netherlands

According to Christina Antoniou, MD, Athens University Sygros Hospital, Athens, Greece, having a "red face" is not always a sign of rosacea.

The clinical symptoms of rosacea include flushing of the central parts of the face and transient to persistent erythema [Powell FC. *N Engl J Med.* 2005]. It is characterized by telangiectasia and papulopustules and usually occurs in adults aged > 30 years old. These symptoms can be mimicked by other skin conditions such as seborrheic dermatitis (an inflammatory skin disorder affecting the scalp, face, and torso), acne vulgaris, perioral dermatitis, cortisone face, contact dermatitis, and polymorphous light eruption (PLE) after sun exposure. Demodicosis (a rare sensitivity to mites that manifests as facial papules and pustules) may also appear similar to rosacea, as can lupus erythematosus and ulerythema ophryogenes. Cutaneous B-cell neoplasms may present facial plaques or patches that mimic granulomatous rosacea or rhinophyma [Barzilai A et al. *Arch Dermatol.* 2012]. B-cell neoplasms may appear in the setting of preexisting rosacea or as a new eruption.

Diagnosis should include a close inspection of the face and a detailed medical history. Differential features of various conditions that present with some similarities to rosacea include, but are not limited to, acne, demodicosis, systemic lupus erythematosus, and PLE. Prof Antoniou suggests the use of a biopsy to confirm a diagnosis when encountering resistance to common therapy.

Noting the lack of sensitive tests to investigate red face sensitivity, Gabriella Fabbrocini, MD, University of Naples Federico II, Naples, Italy, urges dermatologists to perform multiple tests to assess sensitivity before prescribing treatments.

Patients with sensitive skin syndrome (SSS) report exaggerated reactions on skin contact with substances not usually considered irritants that is worse after exposure to dry and cold climates [Berardesca E et al. *Int J Cosmet Sci.* 2013]. SSS is classified as hyperreactive, hypersensitive, or hypersusceptible. Hyperreactors may have a thinner stratum corneum, alterations in vanilloid receptors, and changes in neuronal transmission.

Although 45% of the population report having characteristics of SSS, there have been few studies with objective data. Most of the studies rely on self-diagnosis. The current hypothesis for SSS notes a correlation between sensitive skin and constitutional genetic abnormalities with occupational skin diseases and chronic exposure to irritants as possible triggers. Other hypotheses suggest thinner and/or increased permeability of the stratum corneum, changes in vanilloid receptors, and changes in neuronal transmission as explanations.

Inflammatory conditions related to allergens should be ruled out with patch or photopatch tests before making a diagnosis of SSS. Irritant reactivity tests, bioengineering tests, and sensory testing methods are just a few of the many available tests that can used, none of which are universally accepted. An automatic lesion-counting program is a useful tool for acne severity evaluation [Min S et al. *Skin Res Technol*. 2013]. A common test is the stinging test, in which patients self-report the presence and intensity of a stinging sensation after topical application of lactic acid along the nasolabial fold. A smart phone app is also available to provide objective support for patient responses by measuring erythema photographically and calculating an index of erythema.

Faced with the multiple causes of facial redness, it is often difficult to devise a treatment strategy. Martin Steinhoff, MD, University College of Dublin, Dublin, Ireland, discussed some of the approaches he uses to manage red face symptoms.

Yamasaki and colleagues [*J Invest Dermatol.* 2011; *J Invest Dermatol Proc.* 2011; *Nature Med.* 2007] published several animal studies showing that the activation of proteases leads to signs that resemble rosacea. Proteases are significantly enhanced in inflammatory skin diseases as well as in all subtypes of rosacea and may be an effective therapeutic target for its treatment [Seeliger S et al. *FASEB J.* 2003]. Research also indicates that the ETR and PPR subtypes may be associated more with vasodilation than angiogenesis.

The difficulty of treating rosacea is that vessel function in facial skin is regulated by multiple neural systems including sympathicus, parasympathicus, sensory nerves, and local inflammation.

The diagnosis of rosacea is hampered by the complex activation of the innate and adaptive immune systems, neurovascular dysregulation, and inflammation. A better understanding of the vasodilation mechanism induced by tachykinins released from nerve endings may lead to the next generation of neurokinin receptor antagonists for the treatment of rosacea [Steinhoff MS et al. *Physiol Rev.* 2014].

It is now known that a significant inflammatory infiltrate is detectable in early rosacea.

Early rosacea is also characterized by increases in T cells, macrophages, and mast cells, indicating early activation [Schwab VD et al. *J Investig Dermatol Symp Proc.* 2011]. Early treatment is important because the psychological impact of rosacea is significant on many fronts, including frustration, embarrassment, and low self-esteem.

Red acne can be either common inflammatory acne or inflammatory acne plus diffuse erythema. Giuseppe Micali, MD, University of Catania, Catania, Italy, shared his thoughts regarding the diagnosis and management of this separate entity.

The diffuse erythema seen in some cases of red acne may have several possible causes, including enhanced intrinsic inflammation, side effects from drugs or cosmetics, or other underlying/superimposed "red face" conditions. Recent data suggest that inflammation plays a pivotal role in both the development and severity of acne lesions [Contassot E, French LE. *J Invest Dermatol.* 2014]. Acne products like benzoyl peroxide and retinoids or keratolytic-based cosmetics can also cause diffuse skin irritation and redness, as can discontinuation of inappropriate steroids used to manage acne (Table 1) [Gollnick HP, Zouboulis CC. *Dtsch Arztebl Int.* 2014].

The presence of an underlying chronic "red face" condition such as rosacea, perioral dermatitis, atopic dermatitis, seborrheic dermatitis, and rarely psoriasis may lead to increased diffuse redness in patients with acne. Acute causes of red face such as sunburn, eczema flare, and flushing can also lead to increased redness. Some patients with acne who are prone to flushing and blushing may develop rosacea later in life as well as other "red face" conditions. Acne generally peaks in adolescence but an increased prevalence in adults is observed.

Proper management of "red acne" should include an accurate investigation on the possible causative factors. The use of anti-inflammatory drugs along with a short course of oral steroids (oral prednisolone) followed by oral isotretinoin is suggested in case of diffuse erythema with no apparent causes. In the other cases, avoidance of triggering factors as well as correction of the concomitant "red face" conditions are recommended. Use of mild cleansers, moisturizers, and anti-inflammatory creams may be helpful. Finally, camouflage with specific makeup products is able to minimize redness with positive results.

Ester van Zuuren, MD, Leiden University Medical Centre, Leiden, The Netherlands, presented preliminary results of an updated Cochrane review of 106 randomized controlled trials in adults with rosacea and any type of intervention. Most studies were conducted

Table 1. Side Effects From Topical Acne Products

| Topical Acne Product | Erythema | Stinging/Burning | Desquamation | Xerosis | Bacterial Resistance |
|---|---|---|---|---|---|
| Tretinoin 0.05%[a] | +++ | ++ | ++ | ++ | – |
| Tretinoin 0.025%[a] | ++ | ++ | + | + | – |
| Isotretinoin | + | + | + | + | – |
| Adapalene | + | + | + | + | – |
| Azelaic acid | (+)[b] | ++ | – | + | – |
| Benzoyl peroxide 2.5%[c] | + | + | + | ++ | – |
| Benzoyl peroxide 5%[c] | ++ | ++ | + | ++ | – |
| Erythromycin[d] | – | – | – | – | +++ |
| Clindamycin[d] | – | – | – | – | ++(+)[b] |

[a]New delayed-release formulations cause much less irritation.

[b]Parentheses indicate uncommon effects.

[c]New formulations cause less irritation. All benzoyl peroxide preparations can cause bleaching.

[d]Resistance occurs with monotherapy.

Adapted from Gollnick HP et al. Not all acne is acne vulgaris. *Dtsch Arztebl Int.* 2014;11:301–312. Reproduced with permission from Harald P. Gollnick, MD.

in participants with PPR; the mean study duration was 2 to 3 months.

Among patients with subtype 1, once-daily brimonidine tartrate gel 0.5% reduces moderate to severe erythema over 12 hours (peak effect at 4 to 6 hours) [Fowler J Jr et al. *J Drugs Dermatol.* 2013]. Eight studies addressed laser- and light-based therapies, which appeared to be effective but limited data were provided. The data for metronidazole, azelaic acid, doxycycline, and other laser and/or light therapies were insufficient to draw any conclusions.

For subtype 2, 9 studies noted efficacy with metronidazole; 4 studies noted similar findings for azelaic acid. Ivermectin 1% cream achieved significant ($P < .001$) patient- and physician-assessed improvement and quality-of-life outcomes [Stein L et al. *J Drugs Dermatol.* 2014]. Ivermectin was superior to metronidazole, and patients reported higher satisfaction [Taieb A et al. *Br J Dermatol.* 2014]. Three studies showed effectiveness for the use of oral doxycycline 40 mg with no differences in adverse events vs placebo [Del Rosso JQ et al. *J Am Acad Dermatol.* 2007; Fowler JF Jr. *J Drugs Dermatol.* 2007; Sanchez J et al. *J Am Acad Dermatol.* 2005]. Oral isotretinoin (0.3 mg/kg) is an effective and well-tolerated therapy option as well [Gollnick H et al. *J Dtsch Dermatol Ges.* 2010].

Randomized controlled trial evidence is lacking for pharmacologic treatment of subtype 3; both laser treatment and surgery show good cosmetic results. There is limited evidence for topical cyclosporine 0.05% ophthalmic emulsion over artificial tears for subtype 4.