Ethnicity versus Climate: The Impacts of Genetics and Environment on Rosacea Epidemiology and Pathogenesis

Ana Cristina Diniz Silva[1*] and Saima Ben Fadhel[2]

[1]Department of Postgraduate Studies, Dermatology and Cosmetic Medicine, University of South Wales, UK
[2]Medical Doctor, MSc, UK

[*]**Corresponding author:** Silva ACD, Department of Postgraduate studies, Dermatology and Cosmetic Medicine, University of South Wales, UK; E-mail: adinizsilva@learnaltd.com

Abstract

Rosacea is a chronic inflammatory cutaneous condition, characterized by facial redness in the first stages, followed by papules, pustules and deformities later on the course. The pathogenesis of the disease involves several factors, such as immunologic, infectious and environmental triggers. Genetic predisposing factors are also postulated due to the remarkably positive family history often found. Through a detailed literature review, we aim to qualify and quantify the impact of climatic versus genetic factors on rosacea epidemiology worldwide. Possible associations are here considered, including the higher prevalence of rosacea in fair-skinned individuals of Northern European descent, the influence of the latitude, cold weather, and the diagnostic inaccuracy in people with skin of color. Further, we discuss the roles of cold-induced vasodilation, the skin colonization by *Demodex* mites, and the findings from the most recent genetic studies in this field.

Keywords: Rosacea; Dermatology; Skin rash; Genetics; Epidemiology

1. Introduction

Rosacea is a common chronic inflammatory skin disease affecting 5% to 10% of the world population [1]. This condition alters primarily the vasculature and the pilosebaceous units of the face resulting in variable levels of facial redness, from intermittent flushing, persistent erythema and telangiectasia, to papules, pustules, and ultimately to phymata [2]. Based on its morphological aspects, rosacea can be classified into four major subtypes, as shown in TABLE 1. However, in daily practice, this classification does not reflect the clinical reality, since the different morphological characteristics of those subtypes commonly coexist [1]. Rosacea more often occurs in fair-skinned individuals aged 45 to 60 years old, particularly in populations with a predominant Celtic or northern European heritage. Much less commonly, this condition may also affect people with darker skin phototypes [3].

TABLE 1. **Clinical Classification of Rosacea [1].**

Erythemato-telangiectatic	Centrofacial erythema, telangiectasia, flushing
Papulo-pustular	Centrofacial erythema, variable number of red papules and pustules
Phymatous	Skin thickening, tissue hypertrophy, sebaceous glands hyperplasia
Ocular	Blepharitis, conjuntival redness, ocular dryness, puritus and tearing.

The diversity of rosacea's clinical spectrum has made its etiology and pathophysiology elusive. Studies suggest that the pathogenesis of rosacea involves inappropriate innate and adaptive immune responses to a wide spectrum of biological, environmental and endogenous stimuli leading to an aberrant neurovascular signalling. Skin colonisation with certain microorganisms, such as *Demodex* mites, seems to play a role as one of the various mediators of these events. Well recognised environmental triggers include ultra-violet radiation, alcohol, cold, heat and physical activities. Certain psychological factors such as stress can also cause the disease to flare up. Additionally, a positive family of rosacea is commonly identifiable [3].

Through a detailed literature review, we aim to qualify and quantify the impact of climatic versus genetic factors on rosacea epidemiology worldwide. Possible associations are here considered, including the higher prevalence of rosacea in fair-skinned individuals and the diagnostic inaccuracy in people with skin of colour. Further, we discuss the role of cold-induced vasodilation, the skin colonisation by *Demodex* mites, and the findings from the most recent genetic studies in this field.

2. Epidemiology

2.1. Rosacea in fair-skinned populations

The medical literature is consensual when stating that rosacea has a much higher prevalence among adults of Northern European descent. Sun-sensitive skin, particularly phototypes I and II, correlates with a greater risk for developing rosacea [4]. The prevalence of this condition can be as high as 22% in Europe, according to an Estonian study [5], whereas the global prevalence is estimated in 5.46% in a recently published systematic review [3].

A retrospective study comparing 145 healthy controls and 172 individuals classified either as flushers or diagnosed with rosacea demonstrated that the "cases" had significantly higher chance to have lower skin phototypes (OR 1.75; 95% CI 1.01-3.04; P <0.05) [6]. A large observational study conducted in the UK demonstrated a higher incidence of rosacea in the North of the country, even after age standardisation. This is in accordance with the global trend, as the Irish population is predominantly light-skinned [7]. Another investigation comparing the prevalence of skin diseases in Ghana and the UK demonstrated a prevalence of rosacea of 0% in Ghana, in a significant contrast with the rate of 1.80% found in the UK. This

result marks different prevalences in northern versus southern countries explained by genetic or climatic influences, or maybe justified by the diagnosis insensitivity in dark-skinned subjects [4,8].

2.2. Rosacea in people with skin of colour

Rosacea has been always considered a disease of fair-skinned people, leading to the erroneous perception that this disorder does not occur in people with skin of colour. This point of view is being reconsidered as many reports have shown that people of any racial or ethnic group can be afflicted with rosacea. The estimates of rosacea prevalence in people with higher skin phototypes are quite variable. In African, Asian, Hispanic and Indigenous populations, the higher density of skin pigment masking the facial erythema, in combination with the protective effect of melanin against UV radiation, could explain the lower prevalence of rosacea with darker skin phototypes [1]. The obvious difficulties in recognising telangiectasia and erythema in people with skin of colour increase the chances of under-reporting rosacea in these populations [4].

A large retrospective study that assessed the medical records of nearly 6,700 black African patients, over a period of 8 years, found a very low prevalence of rosacea (0.2%) [9]. In Colombia, where the population comprises a mix of Indigenous, Hispanic and African ethnicities, the overall rosacea prevalence was estimated in 2.85%, which is considerably different from the higher rates found in Europe [10].

According to a robust US ambulatory medical care survey, only 2% of rosacea patients were black, 3.9% were Latino/Hispanic, and 2.3% were Asian. Also in this study, rosacea was considered a primary diagnosis in 2% of whites compared to 0.6% of blacks presenting with skin rash, in 3% of whites and 0% of blacks reporting abnormal skin pigmentation, and in 8.3% of whites compared to only 2.2% of blacks complaining of "other diseases of the skin" [11]. These findings corroborate the postulated higher prevalence of the disease in the fair-skinned population. Similarly, in a nationwide Japanese muticenter study consisting of 67,448 dermatological patients, the diagnosis of rosacea was found in only 150 patients - a quite low prevalence of 0.22%, comparable to what was found by Dlova & Mosan [9], in black populations [12].

3. Pathogenesis and Natural History: Environment versus Genetics

Following the literature review on rosacea epidemiology, a pertinent question comes up to our minds: is rosacea more common in fair-skinned individuals because of genetic factors present in Caucasian populations, or because of the colder temperatures found in the northern areas, especially in Europe? A simplistic way to answer this question would be that, most likely, both mechanisms in conjunction play a role in the pathogenesis and natural history of this condition.

Is it possible, in the light of the available evidence, to separate and quantify the impact from genetics (including ethnicity) and environmental factors on the development of the disease? Initially, we have to describe a phenomenon known as cold-induced vasodilation (CIVD) or the hunting reflex. This refers to a paradoxical vasodilatation that often occurs in the acral areas to modulate the effects of vasoconstriction, which is, in its turn, the first body response to cold [13,14]. Indeed, people living in cold regions often have a stronger CIVD reaction in the peripheral vessels, in comparison to those living in warm or tropical countries. It is presumed that CIVD plays a protective role maintaining tissue integrity and reducing the risks of cold injury. The physiological mechanisms involved in the CIVD reaction remain largely unclear, despite more than 75 years of

research. Such mechanisms may include a simple neuronal reflex, circulating vasodilating substances, disturbances in the neural transmission between sympathetic neurons and the vascular system, and a potential direct effect of cold on vascular smooth muscle activity [13].

The natural history of rosacea involves vasodilation caused by various stimuli including the chronic exposure to cold weather. Persistent vasodilation provokes episodes of flushing, which result in progressive endothelial damage and neoangiogenesis. The chronic inflammation leads to an increased production of vasoactive substances in the dermis, thus potentiating vasodilation and again the inflammatory cascade. Inflammation creates a favourable environment for secondary infection by *Demodex* microorganisms, especially the folliculorum species, which are responsible for the development of papulo-pustular and granulomatous lesions [15].

In addition to the influence of the cold weather on rosacea's pathogenesis, several researches have demonstrated the important role of UV radiation and photo damage as triggers for this disease. UV light exposure and extreme climatic conditions induce the production of free radicals in the skin and contribute to the vascular abnormalities observed in rosacea, i.e., vasodilation, increased capillary permeability, and edema [15].

The existence of a genetic component in rosacea's etiopathogenesis is confirmed by the demonstration of a remarkable familial inheritance for the disease. In 2010, Abram et al. observed that patients diagnosed with rosacea had a higher tendency to exhibit a positive family history to this disorder than did skin-healthy controls (OR 4.31, 95% CI 2.34-7.92, P<0.0001) [6]. It is also interesting to compare the family history between patients with higher versus lower skin phototypes. A Saudi study revealed that approximately 30% of rosacea patients classified as phototypes I and II reported a positive family history, in contrast to only 18% with phototypes IV to VI [16].

In a recent American genome-wide association study including 22,952 individuals of European descent, two single nucleotide polymorphisms (SNPs), the rs763035 and the rs111314066, were identified to be associated with rosacea [17]. In the same study, three major histocompatibility complex (MHC) class II proteins, the human leukocyte antigen (HLA)-DRB1, HLA-DQB1 and HLA-DQA1 were also confirmed to be genetically linked to rosacea. Interestingly, these rosacea-associated HLA genes have been previously identified to be associated with a variety of autoimmune diseases, such as type 1 diabetes mellitus and celiac disease [18].

In a review article, Melnik [19], postulated that rosacea evolved as a mutation in Celts to protect them against life-threatening microbial infections during the Nordic winters. The overexpression of cathelicidin antimicrobial peptide (CAMP) as a response to an upregulated endoplasmic reticulum stress has been shown to play an important role in rosacea pathogenesis. The presence of adequate levels of this antimicrobial peptide provides defense against methicillin-resistant *Staphylococcus aureus* and mycobacterial infections. The insufficient vitamin D-dependent CAMP activation might have been compensated by a mutation that activates an alternative vitamin D-independent CAMP promoter, according to this author.

Epidemiological studies of twins are considered important tools to ascertain the role and the weight of genetic versus environmental factors as etiologic factors for medical conditions. Through the analysis of pre-determined traits in pairs of identical versus fraternal twins, researchers can quantitatively estimate the genetic and the environmental contributions to a certain disease. In a large cohort study of 550 American twin individuals, the authors found a significantly higher correlation

of the rosacea diagnostic scores between identical twin pairs (r = 0.69), in comparison to fraternal twin pairs (r = 0.46, P = .04). Statistical analysis revealed a genetic contribution of approximately 46% to the studied phenotype - the remaining 54% predisposition was accounted for by environmental factors. Among the environmental risk factors, the authors found significant positive correlations between rosacea and UV exposure, age, body mass index (BMI), smoking, alcohol, cardiac comorbidity and history of skin cancer. The single most important environmental variable was UV radiation, according to this study [20].

In the same line of research, Zaidi et al. investigated the facial bacterial microbiome in pair of twins discordant for rosacea [21]. They found a positive relationship between disease's severity and colonisation with *Gordonia* species, and a negative association between severity and the presence of *Geobacillus*. For monozygotic twin pairs, such differences may reflect an important role of environmental contributors to rosacea, most importantly the levels of *Demodex* mites in the skin. For fraternal pairs, overlapping genetic factors should also be considered, including the host immune variables and the local production of antimicrobial peptides.

4. Conclusion

Is rosacea more common in fair-skinned individuals because of genetic factors present in Caucasian populations, or because of the colder temperatures found in the northern regions of the globe, especially in Europe? The answer to this question may not be as simple as one could expect. Rosacea etiopathogenesis is complex and multifactorial. Sun-sensitive skin is only one among many other predisposing factors that include biological elements (immunologic dysregulation, skin colonisation with *Demodex* mites) and environmental triggers (ultra-violet radiation, alcohol consumption, cold, heat and physical activity). A positive family history of rosacea is frequently reported by affected individuals, especially in fair-skinned populations. This provides a formal proof for a genetic contribution to this disease.

On the one hand, cold-induced vasodilation provokes flushing, endothelial damage and neoangiogenesis. The inflammatory cascade that takes place in the skin creates a favourable environment for secondary infection by *Demodex* mites. On the other hand, recent genetic studies have identified single nucleotide polymorphisms and major histocompatibility complex (MHC) class II proteins associated with rosacea, in patients of European descent. Genetic mutations in Celtic populations resultant from the need of protection against life-threatening microbial infections during UV-deficient Nordic winters may also play a key role in rosacea pathogenesis.

We also highlighted that in people with skin of colour, the denser pigmentation impairs the recognition of erythema and telangiectasia. This statement leads to at least three other questions:

1. Can the lower rosacea prevalence in populations with higher skin phototypes be attributed to genetic factors?
2. What is the role of the climate in the rosacea epidemiology in such populations?
3. May these findings simply reflect a diagnostic inaccuracy?

Unfortunately, these questions remain unanswered up to this moment, on the basis of the current evidence. The assessment of the facial microbiome, as a reflect of both genetic and environmental contributing factors, in patients with or without rosacea,

in particular siblings, has been proven to be a powerful tool to elucidate the intricate pathogenesis of this condition, and the differences in its prevalence worldwide.

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