Introduction

Rosacea is a chronic progressive inflammatory disease characterized by a variable degree of facial erythema, telangiectasias, papules and pustules. It is primarily seen in patients aged 30–50 years with more incidence rates in females than males, there are four main clinical subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular. Rosacea fulminans, granulomatous, and steroid-induced are other rosacea variants ***(Pelle et al., 2008).***

Rosacea is easily diagnosed based on clinical features. According to the National Rosacea Society; rosacea can be diagnosed when ≥1 of the following primary features are present on the convex regions of the face: history of frequent flushing, persistent erythema, papules, pustules and telangiectasias. Secondary features include burning, oedema, plaques, dry appearance, ocular manifestations and phymatous changes ***(Crawford et al., 2004).***

The pathogenesis of rosacea remains unclear. Genetic susceptibility, abnormal vascular reactivity, helicobacter pylori infection, Demodex folliculorum infestation, seborrhea, UV light exposure, hypertension, and psychogenic factors are among the proposed etiopathogenic factors; however, none have yet been proven ***(Fimmel et al., 2008).***

Rosacea is an inflammatory skin disease with a chronic course, it was proposed that innate immunity plays a major role in the etiopathogenisis of rosacea and cathelicidin expression is significantly elevated in rosacea skin, compared to healthy skin ***(Yamasaki et al., 2009).*** Besides cathelicidin, **Yamasaki et al.** reported high levels of stratum corneam tryptic enzyme (SCTE), a dermal serine protease, in rosacea lesions. All these findings are evidence that rosacea is an immune disorder, and that cathelicidin and a serin protease play a role in the chronic inflammation characteristic of rosacea ***(Bevins et al., 2007).***

An association between chronic inflammation and Cardiovascular Disease (CVD) was reported ***(Lyndperg et al., 2010).*** Patients with various inflammatory diseases, including rheumatoid arthritis and psoriasis, are reported to have a high risk of developing CVD ***(Mehta et al., 2010).*** Moreover published data links inflammatory nature of rosacea and cardiovascular risk ***(Lyndperg et al., 2010).***

Furthermore, an association between human cathelicidin gene expression and cardiovascular risk factors was reported ***(Benachour et al., 2005).*** Similarly, it was shown that serine proteases play role in all atherosclerotic processes and their inhibitors prevent atherosclerotic plaque progression ***(Bot et al., 2007).***

Few studies reported risk of dyslipidemia and hypertension in rosacea patients which might represent a risk factor for cardiovascular diseases ***(Duman et al., 2014 & Hua et al., 2015).***

Aim of the Work

To study rosacea comorbidities as hypertension, diabetes, dyslipidemia witch might represent cardiovascular risk factors for those patients, and in consequence; increase the risk of developing metabolic syndrome.

ROSACEA

I. Definition of Rosacea

Rosacea is a common chronic skin disorder. It usually affects the central face and across the cheeks, nose, forehead and less commonly may affect non-facial sites ***(Wilkin et al., 2002).***

II. Epidemiology

Rosacea is a common skin disease, however; there are many discrepancies in the results of the epidemiological studies performed over the last few decades. Rosacea affects both sexes, but is almost three times more common in women aged 30 to 50 years, although the development of the complication of rhinophyma is more common in men. It has a peak age of onset between 30 and 60 years, but it can occur rarely in children. Rosacea often affects multiple members of the same family presumably because of their similar complexions and genetic heritage ***(Milliken et al., 2013).***

III. Aetiopathogenesis

The precise aetiology of rosacea is still unknown, and a multi-factorial aetiology is likely. Over the years, many suspected but unconfirmed factors have been reported.

1. Genetic:

Although there are many triggering factors which may be implicated as a cause of rosacea, these triggers are also experienced by healthy persons who never go on to develop the symptoms or signs of rosacea. Therefore, rosaceous individuals may have an inherent sensitivity to these triggering factors, and this predisposition may be genetic ***(Drolet et al., 1992).***

2. Innate Immunity:

The recognition system of the Innate Immunity includes TLR (Toll-like receptors) which responds to environmental stimuli (such as UV, microbes, physical and chemical trauma) and leads to a controlled increase in cytokines and anti-microbial molecules in the skin ***(Gollo et al., 1994).***

One of these anti-microbial molecule is cathelicidin peptide, which is known to have both vasoactive and pro-inflammatory actions. Cathelicidin is expressed in leukocytes (such as neutrophils, monocytes and natural killer [NK] cells) and in keratinocytes ***(Dorschner et al., 2001).***

These cathelicidin peptides promote and regulate leukocyte chemotaxis, angiogenesis, and expression of extracellular matrix components, so would be ideally placed to have a role in rosacea ***(Schmidt et al., 2000).***

Cathelicidin expression in human keratinocytes is regulated by the vitamin D pathway and this could explain why rosacea occurs mainly in the sun exposed areas ***(Peric et al., 2010).***

In keratinocytes, cathelicidin expression increases upon several external stimuli such as infection, injuries, UV irradiation, and permeability barrier disruption which also trigger endoplasmic reticulum (ER) stress which play a novel role in stimulating innate immunity ***(Park et al., 2011).***

3. Vascular Abnormalities:

Many believe that rosacea may be a predominantly vascular disorder because of its association with flushing, redness and visible blood vessels, and certainly, the majority of patients appear to have a vascular element to their disease ***(Tan et al., 2015).***

4. Micro-organisms:

1) Demodex Folliculorum (DF):

Demodex are considered to be commensal organisms in human skin and their numbers increase with the host age. The tendency of rosacea to develop after age of 30 years is paralleled by an increase in demodex mites in facial skin. Many authors believe that demodex folliculorum (DF) has some role in the rosacea development and many studies support this argument ***(Koczulla et al., 2003).***

2) Helicobacter Pylori (HP):

Several studies have suggested a potential relationship between helicobacter pylori (HP) and rosacea, as it has been shown in some studies that the prevalence of HP infection is higher in patients affected by this condition when compared to the general population ***(Akamatsu et al., 1991).***

3) Bacillus oleronius and Staph epidermidis:

Several studies have reported differences in the microbial burden of common skin commensals, such as D folliculorum and S epidermidis, on the skin of healthy subjects and subjects with rosacea, and in bacteria not typically present on the skin, including Helicobacter pylori and Bacillus oleronius. It remains controversial whether this dysbiosis triggers rosacea, or whether the dysbiosis is a response to changes in the skin microenvironment resulting from rosacea's underlying pathophysiology ***(Lacey et al., 2007).***

5. Reactive Oxygen Species (ROS):

The role of ROS in rosacea has been investigated through the actions of the medications used for treating rosacea. Rosacea treatment including oral tetracyclines, topical azelaic acid, topical metronidazole and retinoids all

inhibit the generation of ROS in neutrophils. This results in low level of ROS and supports the hypothesis that ROS involvement is relevant to rosacea ***(Young et al., 2008).***

6. Drugs:

1) Topical Steroids:

It is well known that oral or topical steroids can induce features resembling rosacea. The prolonged use of potent topical steroids on the face often produces symptoms and signs resembling papulopustular rosacea. If application of steroids continues, fixed erythema and telangiectasia develop and may give similar features to idiopathic rosacea ***(Leyden et al., 2015).***

2) Topical Calcineurin Inhibitors:

Topical application of calcineurin inhibitors can cause a rosaceiform dermatitis characterized by numerous small papules and pustules with mild erythema on the face. The distribution of this eruption is generally more widely spread than the centrofacial pattern of papulopustular rosacea ***(Jean et al., 2015).***

3) ***Epidermal Growth Factor Receptor (EGFR) inhibitors:***

There is an increasingly reported development of a papulopustular eruption resembling papulopustular rosacea that results from the use of Epidermal Growth Factor Receptor (EGFR) inhibitors in oncology. This may happen in up to 90% of Patients ***(Lacouture et al., 2006).***

4) ***Other Medications:***

Some other drugs such as amiodarone or vaso-dilating drugs as nifedipine can induce rosacea ***(Akamatsu et al., 1991).***

7. Environmental Factors:

The UV exposure may trigger activation of the innate immune and / or neurogenic effects. Ultraviolet B (UVB) has been shown to induce the production of many immunomodulatory cytokines such as IL-1, IL-4, IL6, IL8, IL10, and TNF-α, while Ultraviolet A (UVA) can inhibit synthesis of collagen and modulate the activity of some Matrix metalloproteinases (MMPs) involved in the degradation and remodelling of the dermal extracellular matrix ***(Yamasaki et al., 2009).***

8. Neurogenic dysregulation:

Four vanilloid receptors and one ankyrin receptor within the transient receptor potential family of cation channels have been shown to be active in rosacea. The fact that many of rosacea's triggers, including temperature changes and spicy food, activate sensory nerves prompted further investigation into the role of the skin's nervous system in rosacea ***(Two et al., 2015).***

9. Abnormal barrier function:

The skin of patients with rosacea has increased transepidermal water loss and decreased epidermal hydration. These changes may be related to increased serine protease levels in rosacea and can be reversed with treatment. As a result of the pathophysiologic changes in rosacea, the skin of these patients has been shown to have a decreased barrier function ***(Two et al., 2015).***

10. Hormonal changes:

Some authors have reported rosacea fulminans occurring abruptly during pregnancy with no history of preceding disease or any other triggering factors. This may resist treatment and persist during pregnancy. However this case improved and responded to treatment after delivery ***(Ciss et al., 2008).***

IV. Diagnosis of rosacea

To date, no diagnostic test for either cutaneous or ocular rosacea, including any serological or histological markers, has been described. Diagnosis of cutaneous rosacea still depends on the clinical symptoms and signs and history review. The diagnosis may be helped by skin biopsy for histology and direct immunofluorescence studies (DIF) to exclude other skin conditions affecting the face ***(Ozcan et al., 2013).***

In 2002, the Committee of the National Rosacea Society (NRS) implemented standard clinical diagnostic criteria for rosacea. Diagnosis can be made clinically by presence of one or more of the below primary features (flushing, non transient erythema, papules and pustules, telangectasia) and may include one or more of the secondary features (burning or stinging, plaques, dry appearance, oedema, ocular manifestations, peripheral location, phymatous changes) ***(Wilkin et al., 2002).***

V. Classification of rosacea

Subtype 1: erythematotelangiectatic rosacea:

Characterized by flushing and persistent central facial erythema. Telangiectases are common but not essential for the diagnosis ***(Yoshioka et al., 2015).***

Subtype 2: Papulopustular rosacea:

It includes persistent central facial erythema with transient papules, pustules, or both in a central facial distribution. Burning and stinging may also be reported ***(Akamatsu et al., 1990).***

Subtype 3: Phymatous rosacea:

This may include thickening skin, irregular surface nodularities and enlargement. Phymatous rosacea occurs most commonly as rhinophyma but may appear elsewhere, including the chin, forehead, cheeks, and ears ***(Miyachi et al., 2015).***

Subtype 4: Ocular rosacea:

Ocular rosacea may include watery or blood shot appearance, foreign body sensation, burning or stinging, dryness, itching, light sensitivity, blurred vision, telangiectasia of the conjunctiva and lid margin, lid and periocular erythema. Blepharitis, conjunctivitis, and irregularity of the eyelid margins also may occur. Meibomian gland dysfunction presenting as chalazion, chronic infection manifested as stye are common. Some patients may experience loss of vision as a result of corneal complications (punctate keratitis, corneal infiltrates, ulcers, marginal keratitis) ***(Wilkin et al., 2004).***

VI. Rosacea variants

1. Granulomatous Rosacea (GR):

Granulomatous rosacea (GR), considered as a distinct variant of rosacea characterized by non caseating epitheloid cell granulomas histologically. It is a rare condition characterized clinically by an eruption of hard reddish papules or small nodules, occurring on a thickened indurated erythematous base ***(Sánchez et al., 2008).***

2. Rosacea Conglobata / Rosacea Fulminans (Pyoderma Faciale):

This is a dramatic development of large facial nodulo-cystic lesions with marked erythema predominantly occurring in young women. The condition is characterized by sudden generalized facial pustular lesions with erythema and facial oedema in patients who have suffered from frequent flushing and sensitive skin but without any other clinical features of rosacea. There is usually no preceding history of acne or rosacea ***(Massa et al., 1982).***

3. Steroid Induced Rosacea:

Steroid-induced rosacea is characterized by centrofacial, perioral, and periocular monomorphic inflammatory papules and pustules distributed in areas that have been chronically exposed to topical steroids,

especially of fluorinated type. The appearance is of a flaming red, scaly, papule covered face (red face syndrome) ***(Litt et al., 1993).***

VII. Differential Diagnosis

There are many other skin diseases which can resemble rosacea and occasionally it is difficult to differentiate between them. Investigations including skin biopsy for histology or DIF, skin allergy tests and additional blood tests may be needed to exclude other differential diagnosis ***(Frank et al., 2009).***

1. Acne vulgaris

Typically, acne vulgaris occurs in younger age group and it is characterized by comedones as well as inflammatory lesions.

2. Seborrhiec dermatitis

Seborrhiec dermatitis is best differentiated by the presence of greasy scales in the nasolibial folds, external ear canals and central eyebrow region.

3. Erythromelanosis faciei and Keratosis Pilaris Rubra

Erythema of lateral cheecks seen in these patients can be confused with erythematotelangiectatic rosacea. The