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Research Progress on Rosacea and Cutaneous Co-Morbidities and Systemic Diseases

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Abstract: Rosacea can be associated with a variety of cutaneous co-morbidities. In addition to skin lesions, rosacea is associated with systemic diseases such as cardiovascular and metabolic diseases, respiratory diseases, gastrointestinal diseases and mental health problems, as well as with the development of some malignant tumors. In addition, ocular disease is a frequent co-morbidity of rosacea. This article reviews recent studies on co-morbidities and systemic diseases of rosacea, which may help to improve the prognosis and quality of life of patients.

Keywords: Rosacea; Co-morbidities; Systemic Diseases.

1. Introduction

Rosacea occurs in the middle of the face and is a chronic inflammatory skin disease that involves the blood vessels of the face and the sebaceous gland units of the hair follicles. Symptoms include flushing or persistent erythema, telangiectasia, papules, pustules and phymatous changes. According to its various clinical characteristics, it is mainly classified into four subtypes: erythematous telangiectasia type, papulopustular type, phymatous type and ocular type. The pathogenesis of rosacea is unclear, but recent studies have shown that it is associated with several factors, including neurally mediated factors, abnormalities in the immune response, infections and genetic predisposition [1]. There is increasing evidence that rosacea is associated with multi-systemic symptoms, including gastrointestinal diseases, metabolic syndrome and cardiovascular diseases. In addition, depression, anxiety and degenerative neurological disorders are highly prevalent in patients with rosacea. Therefore, rosacea should be regarded as a systemic disease [2]. In this article, we review rosacea and skin co-morbidities and other systemic diseases, with the aim of providing a reference for clinical diagnosis and treatment.

1.1. Skin Co-morbidities

Rosacea can be associated with a variety of benign skin diseases and skin tumors. As we age, a number of changes in skin structure and function occur, skin circulation and skin microbiology undergo a series of changes with aging, which are particularly pronounced when estrogen levels decline in women as they enter menopause [3]. Seborrheic dermatitis is a frequent chronic inflammatory skin disease that occurs at the site of seborrhea, and studies have shown that patients with seborrheic dermatitis have a significantly higher risk of developing rosacea, which may be related to local inflammatory responses generated by skin microorganisms, lipid metabolism, and immunity [4].Patients with melasma had an elevated risk ratio (OR=5.1) for rosacea [5], reducing vascular endothelial growth factor (VEGF) and endothelin-1 induced angiogenesis alleviates disease progression[6]. Rosacea was significantly associated with malignant melanoma (OR=6.02), and stratified analyses found that ethnicity may be a risk factor for melanoma progression. However, other studies have shown no association between rosacea and malignant melanoma in Asian populations [7]. A retrospective study conducted in South Korea from 2011 to 2019 found that patients with rosacea had an increased risk of developing actinic keratosis and keratinocyte carcinoma compared with control subjects, with adjusted risk ratios of 6.05 and 2.66, respectively. Ultraviolet (UV) radiation and chronic inflammation of the skin are a possible common pathogenic factor, rosacea, actinic keratosis and keratinocyte carcinoma may share a common susceptibility factor, such as the IRF4 gene [8].

1.2. Cardiovascular and Metabolic Diseases

The development of rosacea and cardiovascular disease (CVD) is associated with chronic inflammation and a pro-inflammatory phenotype, rosacea may contribute to the development of CVD by inducing endothelial dysfunction, which is thought to be the first step in atherosclerosis due to its inflammatory characteristics [9]. Inflammatory markers such as serum IL-1β, IL-6, TNF-α and hs-CRP levels were significantly higher in the rosacea patient group compared to healthy controls [10]. Several studies have shown that patients with rosacea have elevated systolic, diastolic blood pressure, total cholesterol, low-density lipoprotein, increased epicardial fat thickness, higher rates of hypertension, insulin resistance and diabetes mellitus compared to controls [11]. Hypertension, hyperlipidemia and obesity have been shown to play an important role in the pathogenesis of CVD. Another meta-analysis also supported the above findings, and the risk ratios of insulin resistance or diabetes mellitus, high systolic blood pressure, dyslipidemia and CVD in patients with rosacea were 1.18, 1.9, 1.50 and 6.65, respectively [12].However, some studies have shown the opposite, suggesting that patients with rosacea do not have an increased risk of cardiovascular disease, and another study that included 50,442 patients showed that rosacea was associated with hypertension and dyslipidemia, but not ischemic heart disease, stroke or diabetes mellitus [13].The association between smoking and rosacea has not been elucidated [14], but smoking may promote the development of phymatous rosacea and rhinophyma [15].Patients with rosacea are prone to

subclinical cardiovascular disease, and β-blockers are widely used in the treatment of heart failure, hypertension and ischemic heart disease as an essential drug in the treatment of cardiovascular disease, as well as inhibiting vasculogenesis and alleviating the symptoms of vasculogenic dermatoses. It has been shown to be effective in the treatment of papulopustular rosacea. Zinc-alpha2-Glycoprotein (ZAG) is an adipokine involved in the metabolism of lipids, glucose, and insulin. Mean serum ZAG levels were lower in the rosacea group, but the difference was not statistically significant. Serum ZAG levels were significantly lower in rosacea patients with metabolic syndrome, suggesting that ZAG levels are associated with metabolic syndrome in rosacea patients [16].

2. Digestive Diseases

Rosacea is associated with a variety of gastrointestinal diseases, including inflammatory bowel disease (IBD), helicobacter pylori (HP) infection, and celiac disease. The gut-skin axis is one of the mechanisms underlying the pathogenesis of many chronic inflammatory diseases, gastrointestinal health influences skin homeostasis and dynamics through complex interactions between immune, metabolic, and nervous systems, and the gut microbiome is thought to be a major regulator of the gut-skin axis. Small intestinal bacterial overgrowth produces toxic metabolites that induce enterocyte damage and increased intestinal permeability, leading to systemic inflammation [17].Epidemiological studies have shown a potential link between rosacea and IBD [18], both IBD and rosacea have congenital and adaptive immune abnormalities, and they share some common risk factors, such as smoking, obesity and small intestinal bacterial overgrowth [19].The prevalence of HP infection varies among the different types of rosacea, with a higher rate of HP infection positivity in the papulopustular type than erythematous telangiectasia type. A recent meta-analysis showed an increased prevalence of Crohn's disease (OR=1.30) and ulcerative colitis (OR=1.64) in patients with rosacea [20].

3. Neurological and Psychiatric Diseases

A genome sequencing study identified a rare deleterious variant of LRRC4, Sh3pxd2a and SLC26A8, which induces the production of vasoactive neuropeptides in human neuronal cells [21], which are involved in the pathogenesis of rosacea. Some researchers have suggested that increased matrix metalloproteinase (MMP) activity may link the mechanisms between Parkinson's disease and rosacea, with increased expression of MMP-3 and MMP-9 in a mouse model of Parkinson's disease. Tetracycline, a drug commonly used in the treatment of rosacea, is an antibacterial agent that inhibits matrix metalloproteinases, which are also involved in the pathogenesis of atherosclerosis [22].Due to the chronicity of rosacea and its facial manifestations, mental health status is generally poor [23], with a risk ratio of 2.761 for comorbid psychiatric disorders in patients with rosacea, which can take many forms, including phobias and obsessive-compulsive disorder (OCD), in addition to anxiety and depression, with risk ratios for phobias and OCD of 7.841 and 6.389, respectively[24].

4. Respiratory Diseases

More patients with respiratory diseases have rosacea, and the likelihood of comorbidities with rosacea increases with the duration and severity of the disease. FEV 1%, FEV 1/FVC% and FEF 25-75% values were significantly lower in patients with rosacea compared to controls, and FEV 1/FVC% values were correlated with disease severity, suggesting that patients with rosacea may have abnormal respiratory function, and that the severity of the disease is associated with deterioration of respiratory function [25].Obstructive sleep apnea (OSA) is a frequent multisystem sleep disorder, and OSA may be accompanied by autonomic nervous system activation and catecholamine release, which may exacerbate rosacea. Thus, poor sleep may trigger immunomodulatory and intrinsic cutaneous changes in rosacea, with a range of subsequent effects, such as impaired skin barrier defenses and microbial alterations in the skin [26].

5. Malignant Tumors and Ocular Diseases

Tumors of internal organs have also been associated with rosacea. In patients with malignant neoplasms and cancer-free controls, rosacea was significantly associated with an increased risk of breast cancer and glioma, significantly more women than men had rosacea [27], and there was no statistically significant difference between rosacea and the risk of gastric, colorectal and hepatocellular carcinomas [8], with a correlation that needs to be further confirmed. In addition to facial manifestations, more than half of patients with rosacea also have ocular involvement, which can occur in the absence of skin features. The most frequent ocular damage is chronic blepharoconjunctivitis with inflammation of the eyelid margins and meibomian gland dysfunction, and corneal complications include vascularization, ulceration, scarring and rarely perforation [28]. These occur mainly in adult patients, but can also occur in children [29]. A study in Taiwan suggested that diabetic patients with rosacea had a significantly higher risk of developing diabetic macular edema and dry eye disease compared with diabetic patients without ophthalmic surgery, and that the risk of ophthalmic disease continued to increase over time [30].

Some clinicians tend to think of rosacea as a simple facial disfigurement, but actually, systemic associations of rosacea are not limited to the dermatologic realm, and there is increasing evidence that the risk of cardiovascular and metabolic diseases, respiratory diseases, gastrointestinal diseases, mental diseases and malignancies is significantly higher in the rosacea patient population. Clinicians need to be aware of the interactions between rosacea and dermatologic co-morbidities and systemic diseases, and further research is needed to determine whether the presence of systemic diseases exacerbates rosacea, affects the efficacy of rosacea treatments, and whether treatment of co-morbidities may help to ameliorate the condition of rosacea. Therefore, it is important for clinicians to improve their understanding of rosacea and its co-morbidities in order to improve the burden of disease and quality of life for patients with rosacea.

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