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Research advance in rosacea

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Rosacea is a common disease, but its pathogenesis is still poorly understood. For instance, there is a hypothesis in which subtypes develop in an array or another where subtypes are likely to present separately as part of a syndrome. On the other hand, with the improvement in healthcare and diagnosis techniques, more designed studies have been conducted to investigate associated factors of rosacea such as the effect of sunlight, climate and other risk factors. In this study, updates have been included in the classification of epidemiology, aetiology, pathogenesis, subtypes, histology and treatment strategies for rosacea. It is hoped that these will provide new insights into the causes of and treatment for rosacea.

1 Assessment of rosacea severity

Because of 4 subtypes of rosacea classification, it is essential to clarify standard assessment tools valid for different subtypes of rosacea patients. Furthermore, these severity assessment tools are vital for treatment decision making and efficacy appraisal. It has been reported that varied measurement tools used in clinical trials for assessing severity of rosacea[1]. However, the reality is that a reliable and novel assessment methodology is still need to be developed. Moreover, some severity assessment tools depend on patients' perception which might be related to impacts of rosacea on quality of life. It accretes complexity on severity assessing.

2 Quality of life

The clinical severity of rosacea does not correlate with the level of psychosocial distress experienced by the patient. Though considered the mildest form of rosacea, the E-T subtype has significant impacts on quality of life stemming from persistent facial redness. These assessments may be used for various purposes: (1) to increase a patient's self-awareness and empowerment; (2) to increase patient-centeredness in health care; (3) to make an optimal choice for treatment; (4) to monitor treatment over time and determine treatment effectiveness; (5) to improve treatment outcome[2]. The rosacea-specific QOL (21 items) instrument constructs validity by calculating symptoms, functioning, and emotion scale scores which is correlated with self-reported rosacea severity and this can be useful in determining aspects of the disease that are most important or detrimental to an individual patient[3].

3 Epidemiology

Rosacea is a very common chronic disease related all population, but it seems that fair skin population has high prevalences. Rosacea prevalence is very high which is between 2.7 and 10% in patients of northern European or Celtic heritage[4]. The earliest comprehensive population-based prevalence study in rosacea was produced in 1948 and involved 11 000 residents of the Foroe Islands[5]. Abram et al.[6] indicated a genetic component that humans with fair skin (Fitzpatrick skin phenotypes Ⅰ－Ⅱ) arse more frequently to be affected, but African, Asians and Americans can also be seen. Adler reported that African, Latino, or Asian patients comprise approximately 4% of rosacea patients. However, it has reported that during 1989-2002, the incidence of rosacea was about 0.12% among all dermatology patients (109/80,000 all dermatology patients). In one of Taiwanese studies, there were 74 females and 35 males, aged from 15-76years (mean 38 years) and proportion of subtypes from 1 to 4, respectively, 50%, 38%, 11% and 1%[7]. Epidemiological data on rosacea are scarce and controversial, with reported prevalences ranging from 0.09% to 22.00%[8].

Many studies reported there is no difference of incidence between women and men. Nevertheless, most studies support rosacea is more common in women, but when it has developed into phymatous stages, it is more likely in men[9]. In one British recent study, regarding to 60,062 rosacea cases, there were 61.5% female patients, whereas, 80.3% of rhinophyma patients were male[8]. Some researchers have been suggested that direct comparison between studies is confounded by differences in methodology, populations, cultural and social perceptions of disease[10-11].

Regards to the age of incidence, Spoendlin et al.[8] indicated that because there are no strict guidelines for diagnosing rosacea and as rosacea does not typically manifest before the age of 20 year, the rate of their study might be lower than the true

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rates in the UK. However, Kyriakis et al.[12] indicated according to Greek dermatology clinic database study, there was 4% in the youngest age range under 20 years. In Taiwanese study, it reported the patients with ETR and PPR were about 10 years younger than patients with phymatous rosacea and mean age of rosacea was 10 years younger than western reports[7].

4 Aetiology and Pathogenesis

The pathogenic mechanisms which lead to the development of rosacea have not yet been largely understood. Examples of these possible causes as inducing the disease or aggravating its manifestation are genetic predisposition, autoimmune dysregulation, vascular disorders, external factors, dermal matrix degeneration, chemical factors, functional disorders of the pilosebaceous unit, and infectious factors[13]. However, the exact proof of these factors has not been fully conducted.

5 Genetic predisposition

Many skin diseases have been recognized genetic predisposition plays an essential role. Therefore, in practice, it is significant that dermatologists pay attention on collecting family dermal history. 25% of rosacea patients have a family history of the disease which is indicative of a foremost association with familial predisposition[14]. Melnik proposed that, features of rosacea were the result of a genetic mutation that aids people in those areas with no sunlight over winter months to compensate for a lesser production of vitamin D[15]. Yazici et al.[16] found GSTM1 and GSTT1 null genotypes might be as heritable factors of rosacea, although there were only 45 patients with rosacea and 100 control subjects. However, interestingly, Palleschi et al.[17] reported a case, only one of two 51-year-old Caucasian female monozygotic twins had rosacea and they suggested living quality played an important role in occurrence of rosacea.

6 Autoimmune dysregulation

There are many hypothesis of immune pathophysiology of rosacea. One hypothesis seemed acceptably is that neurovascular mechanisms are likely involved in vascular dysregulation characterized by persistent erythema, flushing and telangiectasia, which may be because of overstimulation of the autonomic nervous system in the skin and induction of innate immune responses[18]. Yamasaki et al[19]. stated that Toll-like receptors TLR2 expression is also increased in rosacea, and that it stimulates enhanced KLK5 production in a calcium-dependent manner. In their study, they have indicated that the origin of PPR is a disorder of the immune system, as the initial increase of TLR2 explains why rosacea patients might overreact, although bacterial diversity and quantities are similar between rosacea and normal skin. As already suggested by Bevins and Liu concerning LL-37 and KLK5, in 2007, this hypothesis does not explain the initial increase in TLR2 and, in particular, whether this occurs as a response to specific triggers[20]. In addition, CD31 (blood vessel maker), and LL2-40 (lymphatic vessel marker) has been seen increased in rosacea patients[7]. Compared with healthy skin, the density of TRPV1+ nerve fibers is increased in ETR[18]. Neurovascular dysregulation through TR- PV1may contribute to the early symptoms of rosacea[18].

7 Vascular disorders

The most-cited pathogenetic theory about rosacea has been centered on inherent abnormalities in cutaneous vascular homeostasis. According to this theory, two vasodilatory mechanisms: humoral substances and neural stimuli control the extent of erythema[13]. Reserchers have proposed that dysregulation of thermal mechanisms can cause the vasodilation in rosacea. Wilkin demonstrated that temperature could lead to flushing responses rather than the caffeine of coffee in a 24- ETR-patient study[22]. Hertzman et al.[23] stated that flushing on the central face in ETR and PPR visible could prove the fact that baseline blood flow was higher in the face. The major neuropeptide probably involved in rosacea is substance P. Oates stated that substance P-the mediator played an induced role of flushing in carcinoid, whereas, this was lack of convincible evidence in previous studies. Other mediators included vasoactive intestinal peptide (VIP), gastrin, serotonin, histamine and prostaglandins, because of lack of sufficient experimental support, there still need more evidence to prove. In one study, it showed rosacea is more common seen in patients with menopause and migraine, which are related to vascular disorders[22]. Helfrich et al.[24] indicated telangiectatic photoaging (TP) is distinct from ETR, though vessels are dilated in both TP and ETR. The visibly altered collagen fibrils sourrounding the vessels might contribute vessel dilation in TP, but subhistologic alteration in the ECM, with upregulation of MMPs might induce vessel dilation in ETR. Wilkin[25] approved the study by Helfrich et al. and speculated this study would untie some issues which were identified by himself 21 years ago.

8 Chronic sunlight exposure

It is general thought that sun exposure plays a pivotal role in the process of rosacea. However, there is still no firm verdict. A study of Greek suggested chronic sun exposure had a pathogenic role in rosacea patients[26]. However, there are some speculation of sun exposure is a trigger due to rosacea prevalence in fair phototypes and the predominance of erythema on facial convexities[11].

Moreover, occurrence of the frequent Roascea flares ups in hotter seasons, likewise, elastotic changes due actinic exposure on rosacea histology could be a clue to the role of sunlight in pathogenesis of rosacea[27]. Activation of Vitamin D in human keratinocytes will be stimulated by ultraviolet radition which regulates Cathelicidin LL-37expression in keratinocytes, that's why face is a commonest location for rosacea[28].

However, in one Greek study, they found there was low immunofluorescentic correlation between sunlight and the development of rosacea[26]. In addition, Crawford et al. indicated that unwareness of the sunlight's effect on patients' skin and the appearance changed slowly shoud be considered[13].

9 Dermal matrix degeneration

Neumann et al.[29] indicated that structural changing re- sulted in the formation of telangiectasias and the primary damage

might be due to environmental effect, such as sunlight. They also said the tangle some connective tissue might be secondary to damaged capillaries. By contrast, Motley et al. held deranged connective tissue played a primary role in leading to vascular pathology[30].

10 Chemical factors

Chemical factors are generally discussed between patients with rosacea and dermatologists. Avoiding chemical trigger factors may improve the achievement of treatment. The prevailing evidence at moment is that dietary factors and gastrointestinal factors do not play a primary role in the pathogenesis of rosacea[30]. A British study, regarding to analysis of 60042 rosacea subjects, they determined that alcohol consumption had a slight increased rosacea risk. In addition, smoking was strongly associated with decreased risk of developing rosacea[8]. It is worthy to paying attention on certain medications which can induce flushing in rosacea or rosacea-like dematoses. For example, amiodarone and nicotinic acid have possibilities to lead to flushing in rosacea patients[31]. Topical steroids have been general realized as trigger factor in rosacea-like lesions[32].

11 Functional disorders of the pilosebaceous unit

It is controversy whether the PPR and ETR are follicular based or not. As a result of a study of 108 biopsy specimens, which included 74 patients with PPR and 24 patients with ETR, there were only 20% of the 74 PPR had abnormalities of the hair follicle[30]. Aloi et al. stated that the glandular of rhinophyma is a follicular based process. However, there is still lack of research by subdividing patients into the appropriate subtypes of rosacea[33]. Shi et al. reported it might be more important contributor to the skin barrier dysfunction and development of Papulopustular rosacea altering sebaceous fatty acid profile[34].

12 Microbial organisms

12.1 Demodex mites Over recent decades, there have been many attempts to link the aetiopathogenesis of rosacea to the presence of some micro-organisms on or within the skin, such as Demodex mites and bacteria[26]. Demodex mite is a species of commensal saprophytic mite that olonizes pilosebaceous follicles of human skin[35]. They are universal presence on the skin of human beings, especially nearly 100% in late adulthood. There are many researchers demonstrating that there is a higher density of Demodex mites in the skin of rosacea subjects than control subjects but the significance of this has been disputed. Such immunological conditions favour the development of different types of micro-organisms, including Demodex mites. Other characteristic features of rosacea patients, such as increased vascularization and elevated temperature, may further promote the growth of the organisms[36]. Jarmuda et al.[37] speculated increased Demodex mites might be causative agents of rosacea through multi-mechanisms: they might mechanically block hair follicles, secrete digestive enzymes, destroy the epithelial barrier or trigger reactions of the immune system. However, this is only a hepothesis. Demodex Folleculum releases structural protein known as Chitin, may induce Protease activity via triggering TLR2 activation. Hence, inhibition of this enzyme through blockage of TLR2 activation and/or decreasing the mites number could lessen skin inflammation of Rosacea patients[38]. Moravvej et al.[39] performed prevalence of Demodex mites study in facial biopsy of 75 Rosacea patients as a case group compared to 75 patients of actinic lichen planus and 75 patietns of DLE as a control groups, the density of the mite in case group was a significantly higher than the control groups but, its not exactly clear, whether, rosacea provide a good media for the mite to multiply or the vice versa is the case.

12.2 Helicobater pylori H. pylori is helical gram-negative bacteria which resides in the stomach and generally infects more than half percentage population over the world. Some factors can increase the prevalence of H. pylori, such as age, lower socioeconomic status, overcrowded living qualities, limited hygienic conditions, medications and multi-siblings. It has reported higher prevalence of H. pylori is in Asia and part of Europe than in North America. One Korean H. pylori study reported there were 66.9% of Korean (n=3394) showed seropositivity of H. pylori[40].

H. pylori infection has triggered a significant local inflammatory response and a chronic systemic immune response. Inflammatory mediators might release during the immune reponse to H. pylori infection, such as tumour necrosis factor (TNF)-α, interferon (INF)-γ, leukotrien(LT) C4 and platelet-activating factor (PAF) and might play a role in the pathogenesis of skin disease[41].

Rebora et al.[41] was the first proposer of an association of H. pylori with rosacea. After that, it has been debatable for almost two decades. Several studies have suggested apotential association between H. pylori and rosacea, because the prevalence of H. pylori infection is higher in rosacea patients than in general population.

In one Greek study, there were 100 patients with rosacea and 100 healthy control subjects who were detected antibodies against H. pylori. Immunoglobulin G antibodies against H. pylori were detected in 26 of 63 female patients (41.3%), as well as in 16 of 37 male patients. Compared with antibodies in control subjects which were 46 people had been detected antibodies against H. pylori, there was no significant difference found. However, researchers had found a strong association between H. pylori and rosacea in the group of patients who had not taken any antibiotics[26].

Furthermore, there were several studies had showed the effect of H. pylori eradication in patients with rosacea. For instance, Utas et al.[42] performed a study in 25 patients with rosacea and 87 healthy cases of controlled group. Both of the groups had been detected IgG and IgA antibodies against H. pylori. The result was no statistical difference in seropositivity in either group, but there was a marked improvement of the severity of rosacea at the end of the treatment compared with the initial symptom in rosacea patients who were with H. pylori

infection[42].

Argenziano et al.[43] searched for immunoglobulin IgG and IgA H. pylori antibodies in 48 rosacea patients with or without dyspeptic symptoms. They observed IgG antibodies in 16% of patients without dyspepsia and in 81% of patients with dyspepsia, and IgA antibodies in 6% of patients without dyspepsia and in 61% of patients with dyspepsia. They also found anti-CagA antibodies were positive in 75% rosacea patients with dyspeptic symptoms. They strongly supported a strict correlation between the frequency of the anti-Hp immune response and the rosacea symptom severity can clearly be proved. They hypothesized that rosacea might be related to cagA-positive strains infection. Additionally, a case study has reported a 35-year-old woman with rosacea. This patient also had anti-cagA IgG in her serum, which supported Argenziano's hypothesis[44].

The effect of H. pylori on the pathogenesis of rosacea is still unclear. Gürer et al. described H. pylori had induced the symptoms of rosacea by increasing the synthesis of oxygen metabolites, such as superoxide and proinflammatory cytokines, and thus causing nitric oxide formation. In this included 33 rosacea patients and 20 healthy controlled subjects, H. pylori seropositivity in rosacea patients was higher than the control group, but serum nitrate levels were normal. The authors concluded that nitric oxide is not associated with the inflammatory mechanism of rosacea[45].

By contrast, Herr et al. found no significant difference of prevalences between anti-Hp antibodies in rosacea patients and control cases. They also reported that there was no significant decreasing of skin lesions by treatment of anti-Hp[40]. Similarly, a randomized, double-blind, placebo-controlled study performed the comparison of difference between 20 rosacea patients with H. pylori infection treated and 20 rosacea patients in control group without H. pylori infection treated. Researchers reported there was no short-term beneficial effect on the symptoms of rosacea when H. pylori had been treated for 60 days, so that a casual correlation between H. pylori infection and rosacea could not be supported[46].

13 Other Microbes

There are a robust evidences which claiming the association between Demodex Follicularum and H. Pylori with pathogenesis of rosacea, but recently, evidences emerged regarding involvement of other microbial candidates in rosacea development. For instance, Staphylococcus epidermidis, Chlamydophila pneumoniae, and the Demodex-associated bacteria Bacillus oleronius are blaming by some studies. However, the precise mechanism of their involvement has not well established[47].

Lacey et al. found that, Bacterium Bacillus oleronius isolated from D. Follicularum mites retrieved from the face of a PPR patient. This Bacterium yielded Ag, which was able to induce peripheral blood MNC proliferation in 79% of rosacea patients compared to only 29% of control group. It concluded that antigenic protein of B. oleronius can enhance inflammatory response in PPR patients[48]. Jarmuda et al. conducted a study to evaluate the reactivity of ETR patient's sera to B. oleronius proteins in comparison to control group sera. They found that, serum reactivity to 62 and 83 kDa proteins of B. oleronius among ETR patients reached 82. 6% while in control group it was just 26. 9%. Furthermore, they realized that, sebum level among sera reactive rosacea patients is lower and their D. Follicularum density is higher than control group[49].

Staphylococcus epidermidis which is also predominantly separated from pustules of rosacea patients and could be spread over the face by Demodex mites might have a role in the induction of rosacea. However, no definitive role of bacteria has been recognized yet, but one of the potential lines of its treatment is antibiotics (Tetracycline, Doxycycline), in a suitable environment of over-productive Demodex mites population due to some triggers like harsh wind which damage the skin and Bacteria may colonize it in other word, rocasea may be a bacterial infection in origin[37]. Some researchers considered that when bacteria came out from dead Demodex mites inside pilosebaceous unit, it would lead to activation of neutrophils. Exposure of neutrophils by Bacillus-derived- proteins cause inflammation[50]. However, in a recent systematic review, they could not get any evidence regarding colonization of rosacea skin by Staphylococcus aureus, in contrast to patients with psoriasis and acne[51].

14 Common deterioration triggers

Deterioration factors among rosacea patients are vary from patient to patient. Triggers may include usage of topical facial products, steroids in particular, emotional stress, hot temperature, spicy food, exercise, sun exposure … etc. The negative effect of these factors may range from no effect to mild flushing and deterioration of rosacea symptoms. Discovering and avoiding triggering factors alongside with a good adherence to the medications may help rocasea patient to improve symptoms, avoid flare-ups and prolong remission periods[38]. According to a recent survey conducted by National Rosacea Society (NRS) in the United States from 1, 066 rosacea patients, three of the most common deterioration factors recognized are sun exposure, emotional stress and hot weather[38].

15 Classification of Subtypes

Rosacea is a well recognized chronic cutaneous disorder and characterized by transient or persistent flushing, erythema, papules, pustules and visible blood vessels of central face. In 2002, National Rosacea Society Expert Committee (NRSEC) designed a classified and staged system to standardize diagnostic criteria for clinical, epidemiologic and interventional investigations[13]. This group defined 4 subtypes of rosacea and 1 variant based on clinical features that they divided into primary and secondary.

15. 1 Subtype 1 Erythematotelangiectatic rosacea (ETR) Common presentation of rosacea is generally recognized by flushing and persistent central facial redness. The appearance of cutaneous vascular disorder is common but not elementary feature for a diagnosis of this ETR. Greaves & Burova suggested that it should be investigated to rule out rare conditions that

may be characterized by flushing, if prolonged episodes of severe flushing accompanied by sweating, flushing that is not limited to the face, and, especially, systemic symptoms such as diarrhea, wheezing, headache, palpitations, or weakness. A history of flushing alone is common among patients with ETR[52].

15.2 Subtype 2 Papulopustular rosacea (PPR) Papulopustular subtypehas been characterized by persistent central facial redness with episodic pustules orsmall papulesor both. There is striking contrast of redness between periocular sites and adjacent sites. Patients often present flushing history, but patients experienced flushing is less than patients with ETR. This subtype should be differential diagnosis from acne vulgaris, due to comedones are absent of rosacea. Acne may occur concomitantly in rosacea patients, but sensation of burning and stinging may be helpful in differential diagnosis of papulopustular rosacea.

15.3 Subtype 3 Phymatous rosacea Phymatous rosacea presents thickening skin, irregular surface nodularities, and enlargement. Rhinophyma usually is colloquially described like " drinking nose" by patients and it is a very common presentation. Nevertheless, phymatous rosacea can occur on the chin (gnathophyma), ears (otophyma), and forehead (metophyma). Phymatous rosacea patients may also present patulous follicles and telangiectases. This subtype has commonly been seen in or after some extent combination with ETR or PPR.

15.4 Subtype 4 Ocular rosacea There are some ocular manifestations can be found in rosacea patients, such as blepharitis and conjunctivitis. Interpalpebral conjunctival hyperemia, conjunctival telangiectases, foreign body sensations, burning, stinging, dryness, itching or light sensitivity are frequent signs and symptoms which can be seen in patients with ocular rosacea. Keratitis, scleritis, iritis, andcomplications of such involved manifestations are uncommon, but these can happen. Ocular rosacea may have been prior the cutaneous signs for many years. Also, it has been seen many cases combined ocular manifestations and skin signs simulataneously[53].

16 Other rosacea variants

16.1 Granulomatous rosacea Granulomatous rosacea is a rare separate variant of rosacea, clinically it presents with characterized by eruption of hard yellow, reddish papules or nodules which could be quite severe and lead to scarring. Hisologically also shows characteristic non-caseating epitheloid granulomas.

16.2 Steroid induced rosacea Excessive, regular use of topical corticosteroids, florinated type in particular could lead to rosacea like syndrome.

16.3 Rosacea fulminans Rosacea fulminans is a severe presentations of rosacea features, characterized by multiple red papules, pastules and nodules associated with facial edema and purulent discharge, it is a disease of women only, however, few cases has been reported in men.

17 Rosacea Histology

Biopsy features are mainly dermal changes which reveal chronic inflammation and vascular changes. Biopsy features vary based on clinical subtypes. However, they have chronic solar changes in common.

Lymphocytic channel and vascular dilatations can be noted. Perivascular and interstitial infiltrate of lymphocytes can be seen. Both solar changes and plasma cell predominance is seen in ETR. In PPT, the inflammatory cells are readily visible with significant follicular changes with infiltration of neutrophils, plasma cells and to a lesser extend eosinophils. Remnants of Demodex mites are seen in granulomatous changes resulted from ruptured follicles in some cases[54]. In Phymatous rosacea, there will be some degree of perivascular lymphocytic and neutrophilic infiltration alongside fibrotic changes in dermal skin, the histological features of ocular subtypes is non-specific. The most striking granulomatous changes is seen in a rare variant of rosacea known as (lupus miliaris disseminates faciei, acnitis, acne agminata)[55].

18 Treatment of rosacea

18.1 Objectives of rosacea management (1) Reducing rosacea signs and symptoms, such as erythema, telangiectasia, stinging, and papules and pustules; keeping the texture and beauty of the skin. (2) Achieving and maintaining remission, avoiding flare-ups and exacerbations. (3) Rosacea, regardless of what particular subtype or severity is, it negatively affects the patient's quality of life[2], thus, and measuring the HRQoL should be part of rosacea management through measuring DLQI or, RosaQoL[56]. (4) Psychological impact should be emphasized. Because rosacea is almost confined to the face, it has impacts on psychology of the patient, either through the disease itself and/or the distress of life style changes like avoidance of certain triggering foods and activities like sun exposure and heavy exercise. Hence, dealing with this aspect in management plans in mandatory, while we are managing the patient, we should search for psychological impacts in particular for example, low self-esteem, depression symptoms, feeling of anxiousness to know who should take psychology supportive therapy. (5) Avoiding trigger factors, this one must be achieved through patient's involvement in management plan. Providing sound information resources and explanation of trigger factors like foods and skin care products will lessen patients confusion about their illness and this will improve better rosacea patient-doctor relationship[57] and lastly, better compliance to medications and doctors recommendations. (6) Management strategy should include enquiry about any underline systemic diseases especially inflammatory illnesses in severe cases of rosacea, if it is reluctant to treatments and if you suspect any associated features denoting systemic illness during thorough physical examination. In a recent study, the association between rosacea and a cluster of autoimmune disorders found which were T1DM, celiac disease, multiple sclerosis, and rheumatoid arthritis[58].

18.2 General measures and prevention of flare-ups Treatment of rosacea patient should be tailored for individual patients. However, there are general measures and prevention tips that each rosacea patients should follow regardless of which

subtype and stages of the disease they have in order to resist frequency of relapses as rosacea characterized as a disease of flare-ups and remissions. (1) The patient should be advised to avoid stress. They can try stress relieving techniques, such as Yoga or deep breath. (2) The patient should be advised to limit alcohol intake, hot beverages and spicy foods. (3) Using moisturizers in dry and cold months is important as many rosacea patients experience relapses when they exposure to cold and harsh wind, wearing hat and scarf is recommended. Humectant and occlusive containing moisturizers are recommended as they help to restore skin barrier changes which are occurred in rosacea[59]. (4) In hotter seasons, seeking the shade, wearing broad-brimmed hat, and applying a sunscreen of SPF15 or greater with both UVA and UVB protection are of much help as a sun exposure is the most inciting factors to flare-ups. (5) Immediately treat any medical conditions that aggravate rosacea symptoms like, cough, allergic reactions, cold flu and migrane.

19 Topical therapy

If the main symptoms are papules, pustules or nodules and symptoms are mild, topical treatment, such as metronidazole 0.75% gel or cream, azealic acid 15%, Sulfacetamide 10%-Sulfur 5% are available. Topical ivermectin showed efficacy in moderate to severe PPR. Moreover, a recent study showed topical invermectin had more improvement in quality of life compared with metronidazole[60]. Other alternative topical medications have also been suggested, but there is some controversy. For instance, it is debatable of topical calcineurin inhibitors whether it is effective or not. Otherwise, some reports have showed topical benzoyl peroxide 5%-clindamycin 1% and topical retinoid are beneficial for rosacea, but supporting data is limitied. However, regards to evidence, topical clindamycin or erythromycin are not recommendation for treatment of rosacea, especially, topical antibiotics are not advantage to symptoms of flushing, erythema and telangiectasia.

Kim et al.[61] proposed that, topical 3% tranexamic acid solution could improve epidermal permeability barrier which can be used as an adjuvant therapy to decrease clinical signs of rosacea. Improving barrier functions could improve rosacea features through two mechanisms, firstly decrease the inflammation and secondly decrease the interactions between irritating substances and inner skin[59]. Brimonidine tartrate gel which is an α-2 adrenergic receptor agonist is very effective topical modality treamtnet for persistent erythema in rosacea patients. Brimonidine tartrate gel 0.5% found to be effective and safe treatment for moderate to severe facial erythema in rosacea patients[62].

20 Oral therapy

Oral therapies have been suggested if topical treatment is fail or symptoms are severe. Oxytetracycline 500 mg BD, lymecycline 408 mg OD (both on an empty stomach); doxycycline 40 mg OD are used or erythromycin 500 mg BD is an alternative program. However, anti-inflammatory dose of doxycycline is the only systemic therapy which has been approved by the FDA for treatment of rosacea[63]. It is worth to mention that, in several case reports, metronidazole showed efficacy of treating rosacea[64]. Oral Macrolides are usually prescribed when the tetracyclines are less effective and/or there is contraindicated such as in pregnancy or lactation. Oral erythromycin at a dose of 250mg to 1000mg a day is effective in treatment for PPR[65]. The efficacy of Azithromycin and Clarithromycin is found in a number of studies[66]. Moreover, a study confirms the efficacy of Azithromycin is superior to Doxycycline[67]. Additionally, oral isotretinoin has been reported it may be effective in severe rosacea or recurrent cases[68]. While patients have significant ocular problems, oral isotretinoin should be avoided.

21 Skin care recommendations and other management

Using of a gentle cleanser and moisturizers, and sunscreen are important components of daily skin maintenance in patients with rosacea. Considering the impacts on patient QoL, camouflage should be suggested for improving the appearance. If patients have ocular problems, artificial tears and other symptomatic treatment for eyes are necessary. Severe cases of ocular symptoms should be referred to ophthalmologists. Last but not least, there are some reports show it is effective and essential using laser therapy such as pulsed-dye laser and intensive pulsed light to treat persistant erythema or telangiectasia. However, laser and light-based therapies are still in the situation of low-quality evidence[69].

22 Laser treatment and surgery

Laser has role in rosacea treatment, particularly for reducing redness, telangiectasia and flushing of the face. Intense pulsed-light therapy (IPL), which penetrates deep and has different targets such as melanin and hemoglobin, it's been used as facial rejuvenation and improve vascular lesions in rosacea patients[70]. IPL, in another study shows decrease blood flows, telengiectasia and intensity of erythema by 30%, 29% and 21% respectively[71].

Pulsed dye laser (PDL), selectively targets vascular lesions owing to selective absorption of the light by oxyhemoglobin[72]. PDL demonstrated decrease in erythema and telangiectasia in rosacea patients[73-74]. Moreover, a recent study proves that, PDL, improves quality of life in ETT rosacea patients[75].

Other types of laser which show efficacy in rosacea treatments are, CO2 laser and erbium: yttrium-aluminum-garnet laser. Neodymium: yttrium- aluminum-garnet laser Potassium-titanyl phosphate laser[76]. A recent study shows that, fractional microneedling radiofrequency FMR demonstrated the clinical and histological improvement in rosacea patients, they recommend FMR as an alternative or adjuvant modality of rosacea treatment[77]. Co2 laser has been found to be effective for treating irregular nodular rhinophyma since 1987[78]. In addition, treatment of ocular rosacea, is beyond the scope of this paper and it is prudent to refer these patients to ophthalmologists.

23 Conclusion

High-quality updated knowledge can be helpful for clinicians' decision making, improving clinical practice and allowing

for patient preferences. Treatment decisions should be based on the severity and the specific subtype(s) of rosacea involved. Treatment can be given comprising a combination of medications. Additionally, rosacea patients' quality of life should be considered before and during treatment. Finally, the Chinese translation of rosacea "酒渣鼻" should be changed to avoid misapprehensions surrounding this condition.

参考文献

[1] Hopkinson D, Moradi TS, Alinia H, et al. Assessment of rosacea severity: a review of evaluation methods used in clinical trials[J]. J Am Acad Dermatol, 2015, 73(1): 138-143.

[2] van Cranenburgh OD, Prinsen CA, Sprangers MA, et al. Health-related quality-of-life assessment in dermatologic practice: relevance and application [J]. Dermatol Clin, 2012, 30(2): 323-332.

[3] Nicholson K, Abramova L, Chren MM, et al. A pilot quality-of-life instrument for acne rosacea[J]. J Am Acad Dermatol, 2007, 57(2): 213-221.

[4] Webster GF. Rosacea[J]. Med Clin North Am, 2009, 93(6): 1183-1194.

[5] Lomholt G. Prevalence of skin diseases in a population; a census study from the faroe islands [J]. Dan Med Bull, 1964, 11(11): 1-7.

[6] Abram K, Silm H, Oona M. Prevalence of rosacea in an Estonian working population using a standard classification[J]. Acta Derm Venereol, 2010, 90(3): 269-273.

[7] Yang CC, Hsieh FS, Lee JY. Pyoderma gangrenosum complicated by ecthyma gangrenosum[J]. Br J Dermatol, 2004, 150(5): 1025-1026.

[8] Spoendlin J, Voegel JJ, Jick SS, et al. A study on the epidemiology of rosacea in the U. K[J]. Br J Dermatol, 2012, 167(3): 598-605.

[9] Augustin M, Herberger K, Hintzen S, et al. Prevalence of skin lesions and need for treatment in a cohort of 90 880 workers[J]. Br J Dermatol, 2011, 165(4): 865-873.

[10] Chosidow O, Cribier B. Epidemiology of rosacea: updated data[J]. Ann Dermatol Venereol, 2011, 138 Suppl 2: S124-128.

[11] Elewski BE, Draelos Z, Dreno B, et al. Rosacea - global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group [J]. J Eur Acad Dermatol Venereol, 2011, 25(2): 188-200.

[12] Kyriakis KP, Palamaras I, Terzoudi S, et al. Epidemiologic aspects of rosacea[J]. J Am Acad Dermatol, 2005, 53(5): 918-919.

[13] Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification [J]. J Am Acad Dermatol, 2004, 51(3): 327-341.

[14] Abram K, Silm H, Maaroos HI, et al. Risk factors associated with rosacea[J]. J Eur Acad Dermatol Venereol, 2010, 24(5): 565-571.

[15] Melnik BC. Rosacea: the Blessing of the celts-an approach to pathogenesis through translational research[J]. Acta Derm Venereol, 2016, 96(2): 147-156.

[16] Yazici AC, Tamer L, Ikizoglu G, et al. GSTM1 and GSTT1 null genotypes as possible heritable factors of rosacea[J]. Photodermatol Photoimmunol Photomed, 2006, 22(4): 208-210.

[17] Palleschi GM, Torchia D. Rosacea in a monozygotic twin [J]. Australas J Dermatol, 2007, 48(2): 132-133.

[18] Steinhoff M, Buddenkotte J, Aubert J, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea[J]. J Investig Dermatol Symp Proc, 2011, 15(1): 2-11.

[19] Yamasaki K, Gallo RL. Rosacea as a disease of cathelicidins and skin innate immunity[J]. J Investig Dermatol Symp Proc, 2011, 15(1): 12-15.

[20] Bevins CL, Liu FT. Rosacea: skin innate immunity gone awry[J]. Nat Med, 2007, 13(8): 904-906.

[21] Gomaa AH, Yaar M, Eyada MM, et al. Lymphangiogenesis and angiogenesis in non-phymatous rosacea[J]. J Cutan Pathol, 2007, 34(10): 748-753.

[22] Wilkin JK. Oral thermal-induced flushing in erythematotelangiectatic rosacea[J]. J Invest Dermatol, 1981, 76(1): 15-18.

[23] Hertzman AB, Randall WC. Regional differences in the basal and maximal rates of blood flow in the skin[J]. J Appl Physiol, 1948, 1(3): 234-241.

[24] Helfrich YR, Maier LE, Cui Y, et al. Clinical, histologic, and molecular analysis of differences between erythematotelangiectatic rosacea and telangiectatic photoaging[J]. JAMA Dermatol, 2015, 151(8): 825-836.

[25] Wilkin JK. Erythematotelangiectatic rosacea and telangiectatic photoaging: same, separate, and/or sequential? [J]. JAMA Dermatol, 2015, 151(8): 821-823.

[26] Lazaridou E, Fotiadou C, Ziakas NG, et al. Clinical and laboratory study of ocular rosacea in northern Greece[J]. J Eur Acad Dermatol Venereol, 2011, 25(12): 1428-1431.

[27] Powell FC. Clinical practice. Rosacea[J]. N Engl J Med, 2005, 352(8): 793-803.

[28] Reinholz M, Ruzicka T, Schauber J. Cathelicidin LL-37: an antimicrobial peptide with a role in inflammatory skin disease[J]. Ann Dermatol, 2012, 24(2): 126-135.

[29] Neumann E, Frithz A. Capillaropathy and capillaroneogenesis in the pathogenesis of rosacea[J]. Int J Dermatol, 1998, 37(4): 263-266.

[30] Marks R, Harcourt-Webster JN. Histopathology of rosacea[J]. Arch Dermatol, 1969, 100(6): 683-691.

[31] Wilkin JK. Why is flushing limited to a mostly facial cutaneous distribution[J]. J Am Acad Dermatol, 1988, 19(2 Pt 1): 309-313.

[32] Leyden JJ, Thew M, Kligman AM. Steroid rosacea[J]. Arch Dermatol, 1974, 110(4): 619-622.

[33] Aloi F, Tomasini C, Soro E, et al. The clinicopathologic spectrum of rhinophyma[J]. J Am Acad Dermatol, 2000, 42(3):468-472.

[34] Shi VY, Leo M, Hassoun L, et al. Role of sebaceous glands in inflammatory dermatoses[J]. J Am Acad Dermatol, 2015, 73(5):856-863.

[35] Holmes AD. Potential role of microorganisms in the pathogenesis of rosacea[J]. J Am Acad Dermatol, 2013, 69(6):1025-1032.

[36] Whitfeld M, Gunasingam N, Leow LJ, et al. Staphylococcus epidermidis: a possible role in the pustules of rosacea [J]. J Am Acad Dermatol, 2011, 64(1):49-52.

[37] Jarmuda S, O'Reilly N, Zaba R, et al. Potential role of Demodex mites and bacteria in the induction of rosacea[J]. J Med Microbiol, 2012, 61(Pt 11):1504-1510.

[38] Lavers I. Rosacea: clinical features and treatment[J]. Nurs Stand, 2016, 30(31):52-60.

[39] Moravvej H, Dehghan-Mangabadi M, Abbasian MR, et al. Association of rosacea with demodicosis[J]. Arch Iran Med, 2007, 10(2):199-203.

[40] Herr H, You CH. Relationship between Helicobacter pylori and rosacea: it may be a myth[J]. J Korean Med Sci, 2000, 15(5):551-554.

[41] Rebora A. Rosacea[J]. J Invest Dermatol, 1987, 88(3 Suppl):S56-60.

[42] Utas S, Ozbakir O, Turasan A, et al. Helicobacter pylori eradication treatment reduces the severity of rosacea[J]. J Am Acad Dermatol, 1999, 40(3):433-435.

[43] Argenziano G, Donnarumma G, Iovene MR, et al. Incidence of anti-Helicobacter pylori and anti-CagA antibodies in rosacea patients[J]. Int J Dermatol, 2003, 42(8):601-604.

[44] Mini R, Figura N, D'Ambrosio C, et al. Helicobacter pylori immunoproteomes in case reports of rosacea and chronic urticaria[J]. Proteomics, 2005, 5(3):777-787.

[45] Gurer MA, Erel A, Erbas D, et al. The seroprevalence of Helicobacter pylori and nitric oxide in acne rosacea[J]. Int J Dermatol, 2002, 41(11):768-770.

[46] Bamford JT, Tilden RL, Blankush JL, et al. Effect of treatment of Helicobacter pylori infection on rosacea[J]. Arch Dermatol, 1999, 135(6):659-663.

[47] Holmes AD. Potential role of microorganisms in the pathogenesis of rosacea[J]. J Am Acad Dermatol, 2013, 69(6):1025-1032.

[48] Lacey N, Delaney S, Kavanagh K, et al. Mite-related bacterial antigens stimulate inflammatory cells in rosacea[J]. Br J Dermatol, 2007, 157(3):474-481.

[49] Jarmuda S, McMahon F, Zaba R, et al. Correlation between serum reactivity to Demodex-associated Bacillus oleronius proteins, and altered sebum levels and Demodex populations in erythematotelangiectatic rosacea patients [J]. J Med Microbiol, 2014, 63(Pt 2):255-262.

[50] McMahon F, Banville N, Bergin DA, et al. Activation of neutrophils via IP3 pathway following exposure to Demodex-associated bacterial proteins[J]. Inflammation, 2016, 39(1):425-433.

[51] Totte JE, van der Feltz WT, Bode LG, et al. A systematic review and meta-analysis on Staphylococcus aureus carriage in psoriasis, acne and rosacea[J]. Eur J Clin Microbiol Infect Dis, 2016, 35(7):1069-1077.

[52] Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea [J]. J Am Acad Dermatol, 2002, 46(4):584-587.

[53] Borrie P. Rosacea with special reference to its ocular manifestations[J]. Br J Dermatol, 1953, 65(12):458-463.

[54] Cribier B. Rosacea under the microscope: characteristic histological findings[J]. J Eur Acad Dermatol Venereol, 2013, 27(11):1336-1343.

[55] Nishimoto J, Amano M, Setoyama M. The detection of Propionibacterium acnes signatures in granulomas of lupus miliaris disseminatus faciei[J]. J Dermatol, 2015, 42(4):418-421.

[56] van der Linden MM, van Rappard DC, Daams JG, et al. Health-related quality of life in patients with cutaneous rosacea: a systematic review[J]. Acta Derm Venereol, 2015, 95(4):395-400.

[57] Alinia H, Moradi TS, Farhangian ME, et al. Rosacea patients seeking advice: qualitative analysis of patients' posts on a rosacea support forum[J]. J Dermatolog Treat, 2016, 27(2):99-102.

[58] Egeberg A, Hansen PR, Gislason GH, et al. Clustering of autoimmune diseases in patients with rosacea[J]. J Am Acad Dermatol, 2016, 74(4):667-672.

[59] Addor FA. Skin barrier in rosacea[J]. An Bras Dermatol, 2016, 91(1):59-63.

[60] Taieb A, Ortonne JP, Ruzicka T, et al. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial[J]. Br J Dermatol, 2015, 172(4):1103-1110.

[61] Kim MS, Chang SE, Haw S, et al. Tranexamic acid solution soaking is an excellent approach for rosacea patients: a preliminary observation in six patients[J]. J Dermatol, 2013, 40(1):70-71.

[62] Fowler J, Jarratt M, Moore A, et al. Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies[J]. Br J Dermatol, 2012, 166(3):633-641.

[63] Del RJ, Leyden JJ. Status report on antibiotic resistance: implications for the dermatologist[J]. Dermatol Clin, 2007, 25(2):127-132.

[64] Leyden JJ, Del RJ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance[J]. Cutis, 2007, 79(6 Suppl):9-23.

[65] Baldwin HE. Systemic therapy for rosacea[J]. Skin Therapy Lett,2007,12(2):1-5,9.
[66] Bakar O,Demircay Z,Gurbuz O. Therapeutic potential of azithromycin in rosacea[J]. Int J Dermatol,2004,43(2):151-154.
[67] Akhyani M,Ehsani AH,Ghiasi M,et al. Comparison of efficacy of azithromycin *vs*. doxycycline in the treatment of rosacea:a randomized open clinical trial[J]. Int J Dermatol,2008,47(3):284-288.
[68] Hoting E,Paul E,Plewig G. Treatment of rosacea with isotretinoin[J]. Int J Dermatol,1986,25(10):660-663.
[69] van Zuuren EJ,Fedorowicz Z. Interventions for rosacea:abridged updated Cochrane systematic review including GRADE assessments[J]. Br J Dermatol,2015,173(3):651-662.
[70] Campolmi P,Bonan P,Cannarozzo G,et al. Intense pulsed light in the treatment of non-aesthetic facial and neck vascular lesions:report of 85 cases[J]. J Eur Acad Dermatol Venereol,2011,25(1):68-73.
[71] Mark KA,Sparacio RM,Voigt A,et al. Objective and quantitative improvement of rosacea-associated erythema after intense pulsed light treatment[J]. Dermatol Surg,2003,29(6):600-604.
[72] Jasim ZF,Woo WK,Handley JM. Long-pulsed (6-ms) pulsed dye laser treatment of rosacea-associated telangiectasia using subpurpuric clinical threshold[J]. Dermatol Surg,2004,30(1):37-40.
[73] Bernstein EF,Kligman A. Rosacea treatment using the new-generation,high-energy,595 nm,long pulse-duration pulsed-dye laser[J]. Lasers Surg Med,2008,40(4):233-239.
[74] Neuhaus IM,Zane LT,Tope WD. Comparative efficacy of nonpurpuragenic pulsed dye laser and intense pulsed light for erythematotelangiectatic rosacea[J]. Dermatol Surg,2009,35(6):920-928.
[75] Bonsall A,Rajpara S. A review of the quality of life following pulsed dye laser treatment for erythemotelangiectatic rosacea[J]. J Cosmet Laser Ther,2016,18(2):86-90.
[76] Weinkle AP,Doktor V,Emer J. Update on the management of rosacea[J]. Plastic Surgical Nursing,2015,35(4):184-202.
[77] Min S,Park SY,Yoon JY,et al. Fractional microneedling radiofrequency treatment for acne-related post-inflammatory erythema[J]. Acta Derm Venereol,2016,96(1):87-91.
[78] Roenigk RK. CO_2 laser vaporization for treatment of rhinophyma[J]. Mayo Clin Proc,1987,62(8):676-680.

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抗 N-甲基-D-天冬氨酸受体脑炎的研究进展

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抗 N-甲基-D-天冬氨酸受体(N- methyl-D-aspartate receptor,NMDAR)脑炎属免疫相关性脑炎,是新近发现且日渐受到关注的边缘性脑炎(limbic encephalitis,LE)的一种,目前其发病机制尚不明确,可能为抗 NMDAR 抗体影响兴奋性谷氨酸信号转导所致,临床表现复杂多变,在血清和(或)脑脊液中检出抗 NMDAR 抗体则具备诊断价值。主要累及育龄期女性,常伴有卵巢肿瘤,免疫治疗有效,预后一般较好。2005 年 Vitaliani 等[1]报道 4 例卵巢畸胎瘤(ovarian teratoma,OT)年青女性患者出现认知功能降低、记忆障碍、精神行为异常、意识水平改变及通气不足的一组临床表现,推测也许是一种新型的肿瘤相关性 LE,又称为"畸胎瘤相关性脑炎"。2007 年 Dalmau 等[2]研究发现临床表现类似(包括记忆缺失、行为异常、认知障碍和癫痫发作)的患者共同存在一种抗体为抗海马神经元胞膜(或称群神经纤维网抗原)表达的 NMDAR 抗体,主要亚基为 NMDAR1/NMDAR2(NR1/NR2)二聚体,并提出了肿瘤相关性自身免疫性抗 NMDAR 脑炎的诊断。目前,国际多中心 577 例的病例队列研究显示[3],除年轻女性外,儿童、青少年、男性(约占 11%)也可累及,大多数的男性患者未发现潜在的肿瘤,约 50%女性患者未伴有卵巢肿瘤。随着报道的增多及检查的深入,此病越来越受到神经内科、精神科、肿瘤科的重视。因此,本文就抗 NMDAR 脑炎发病机制、临床表现、辅助检查及治疗等进展进行综述。

1 流行病学

本病多累及年青女性患者,常伴发肿瘤,大多数为成熟 OT,也有少部分为小细胞肺癌、纵隔畸胎瘤。发病率不详,加利福尼亚脑炎项目发现,抗 NMDAR 脑炎占脑炎患者的 4.2%,这超过了任何特定的病毒导致脑炎患者的数量,此病常发于 30 岁以下的患者[4]。在英国的一份前瞻性研究中显示,脑炎患者中,自身免疫相关性脑炎发病率仅次于急性播散性脑脊髓炎,位居第 2[5]。在台湾最近的一份研究中显示,不明原

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