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Prostanoid Modulation Of Vasomotor Reactions In Rosacea.

Anas Sarayreh Atalla Salem¹, Larisa V. Kuts¹, Vasily A. Bocharov², Mykhailo M. Lebediuk²,
Veronika V. Bocharova², and Nina B. Prokofyeva^{2*}.

¹Sumy State University (Sumy, Ukraine).

²Odesa National Medical University (Odessa, Ukraine).

ABSTRACT

Rosacea is a chronic inflammatory skin disease. Numerous aspects of etiology and pathogenesis of this dermatosis remain not clear. The aim of this research is to study the frequency and characteristics of the first clinical signs and the further course of rosacea in women, to specify the role of prostaglandins in the development of vasomotor reactions in patients. We observed 52 women with rosacea aged 20-53 years who had a history of sudden short facial flushing accompanied by skin redness of the nasolabial region and mild local heat/ warmth sensations. They subsequently recurred with the onset of erythema (transient, persistent), telangiectasias, papules and pustules influenced by various provoking factors. The enzyme immunoassay testing of all patients showed a definite significant increase in the serum content of prostaglandins E2 and F2 α . Their level correlated with the duration and the stage of the disease as well as with the presence of flushing during the treatment of patients. Prostaglandins can play the role of both inflammatory mediators and modulators of vasomotor reactions at the peripheral (cutaneous microvasculature) and central levels (structure of the hemodynamic center), which dictates the need for an integrated approach to the treatment of the patients.

Keywords: rosacea in women, prostaglandins, modulation of effects.

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**Corresponding author*

INTRODUCTION

Rosacea is a chronic inflammatory skin disease predominantly affecting the face, observed in 5 to 10% of the world's population [1]. Uncertainty of numerous etiology aspects, complexity of the pathogenesis, clinical associations of this disease with various comorbidities of skin, internal organs, and body systems necessitate systemic therapy, which often appears not very effective, is accompanied by complications, and leads to a recurrence of the process in open areas of skin significantly affecting the quality of life of patients [2]. Modern peculiarity of rosacea in women is its more frequent occurrence at the reproductive age, syndromic nature of early manifestations of this disease (flushing, changes in the skin), to which neither patients nor doctors pay enough attention [3]. Such nature of clinical manifestations of the disease remains poorly studied as well as the role of biologically active compounds that can thoroughly influence the occurrence of disorders in endocrine, vascular, nervous systems and skin (in particular prostaglandins). The necessity to differentiate early signs and symptoms of rosacea from similar changes of a different genesis (associated with climax, migraine and others) in the skin and various body systems [4, 5] dictates the expediency of further study of this topical issue in order to prevent the progression of the pathological process and to make timely correction in the comprehensive therapy of patients [6, 7].

The study is a part of an integrated research work "Substantiation of modern approaches to diagnosis, treatment and prevention of chronic dermatoses and sexually transmitted diseases" (state registration number 0116U008932).

Aims. The aim of this research is to study the frequency, clinical manifestations of "flushing" in women with rosacea; to determine the role of prostaglandins in the development of local and central vasomotor reactions in different courses of dermatosis.

MATERIAL AND RESEARCH METHODS

We carried out a clinical and laboratory examination of 52 women with rosacea (aged 20-53 years) with the disease duration ranging from 2 to 11 years. In our work with patients we followed accepted international recommendations "On compliance with ethical standards" for research with human participation (ethics committee approval; informed consent of the examined patients; compliance of the studies with the ethical standards of the Declaration of Helsinki 1964 and its later amendments).

The inclusion criteria for participation in the study were: women over 20 with mild erythematotelangiectatic and papulopustular rosacea; the ability of the patients to adequately cooperate with the doctor.

The exclusion criteria were: complicated forms of rosacea in patients (ocular form, rhinofyma); manifestations of infectious diseases during the examination, acute exacerbation of chronic diseases of organs and systems, decompensated accompanying pathology; endocrine disorders; taking medications not recommended for systemic treatment in less than a month before and during the study; participation of the patients in another clinical trial.

The diagnosis was made in accordance with the recommendations of the National Rosacea Society Expert Committee (USA, 2002).

The level of prostaglandins (PGE2 and PGF2alpha) in patients was determined in blood serum by the enzyme immunoassay with the use of such reagents as "Prostaglandin E2 (PGE2)", "Prostaglandin F2 alpha (PGF2 alpha)" BCM Diagnostics (USA) on a plate reader "Multiscan FX" (Finland).

Data processing was carried out using parametric and nonparametric methods (we determined the arithmetic average, its error, the reliability of the difference of the studied indices: the Mann-Whitney U-test, the Wilcoxon rank sum test. Results were considered statistically significant if $p < 0.05$. We used licensed analytics software product "STATISTICA® for Windows 6.0", No.AXXR712D833214FAN5).

RESULTS AND DISCUSSION

It was found that all examined patients had sudden facial flushes lasting for several minutes, accompanied by various visible and perceptible clinical manifestations (skin redness of limited areas more often observed in the nasolabial region, moderate sensation of warmth or mild local heat). Almost all patients could not definitely name the factors causing the first flushing and did not ask for medical help as symptoms and subjective sensations disappeared quickly and completely. Most patients (38) already associated the second and subsequent flushing episodes with the action of some triggering factors (more often external ones), and in 14 out of 38 cases with menstrual disorders. The most frequent external triggering dietary factors were hot drinks, spicy dishes and alcohol. Triggering effects of increased ultraviolet irradiation were observed in 6 patients, local heat exposure (from the kitchen stove) – in 5, cold – in 4, other irritants (rain, wind) – in 3 patients. In addition to the above mentioned endogenous factors (associated with menstrual disorders), some patients (6) noted flushing after emotional excitement.

The duration of repeated flushing episodes gradually increased (up to several hours), areas of facial redness spread outside the nasolabial region (on the forehead, cheeks, chin), subjective manifestations also became somewhat more intense – except for local sensations warmth/heat some patients noted moderate itching and/or skin crawling sensation in the foci of redness, which made them rub, stroke or scratch these places.

Almost all patients self-medicated when the first signs of flushing appeared; (many – with the subsequent exacerbations of the disease) using various external agents (both cosmetic and medicinal and, above all, corticosteroid creams).

After a range of relapses and remissions of such flushing (despite self-medication and – subsequently – standard treatment) the patients showed clear signs of rosacea.

Patients with the disease duration of up to 2 years (26) developed the main and additional symptoms of the erythematotelangiectatic rosacea (subtype) (erythema of various types, superficial and localized telangiectasias, areas of moderate infiltration in certain areas of facial skin). Patients with the disease over 2 years (26) also had manifestations of papulopustular rosacea, the areas of erythema on the face became larger and spread to the décolleté in some patients, the network of telangiectasias also increased.

The prostaglandins (PG) level in blood serum (both PGE2 and PGF2α) was elevated in all patients (compared to healthy controls – 20 women of a similar age group), but they were different in women with preserved flushing during the supervision of the patients (Table 1).

Table 1. Serum prostaglandin (PG) level (pg / ml) in women with rosacea and in healthy controls

Clinical manifestations of flushing	PGE2	PGF2α
erythematotelangiectatic subtype (n=26)		
present (n=12)	804,1±32,0	159,1±10,3
absent (n=14)	625,4±35,1	129,3±10,1
papulopustular subtype (n=26)		
present (n=8)	670,5±18,8	129,3±13,1
absent (n=18)	536,1±16,6	109,3±10,8
healthy controls (n=20)		
absent (n=20)	446,7±10,2	99,4±4,2

According to the data in the table in erythematous and telangiectatic rosacea in women the levels of PGE2 and PGF2α on average were elevated compared to the indices of the healthy controls both in patients with and without flushing, but differed significantly among these subgroups (p<0.05). In papulopustular subtype the same reliability of the difference of these prostaglandin levels was observed in the compared

groups and subgroups of women with rosacea. However, the values of the changed indices were less marked which indicates the correlation dependence of changes in prostaglandin levels on the duration of the disease. Taking into account that these 2 classes of prostaglandins provide opposite effects in the human body we can state that the compensatory mechanisms of the balance of their effects in restoring disturbed homeostasis of the body are disrupted, which is considered a promising direction in the study of the pathogenesis of this dermatosis [8, 9].

The impact of a range of negative factors can affect the regulatory mechanisms ensuring the balance of physiological correlation of the types of hormones produced by theca tissue and ovarian granulosa. Therefore, besides steroid sex hormones other hormones of a different origin are engaged including metabolites (prostaglandins) – hormone-like biologically active compounds synthesized also by the ovaries. In addition to the functions of regulators of vascular tone, inflammation prostaglandins also play a modulatory role in relation to many other biologically active compounds including hormones, in particular biosynthesis and secretion of the luteinizing hormone-releasing factor by neurons of the medial basal hypothalamus. Therefore they can affect the complex chain of neuroendocrine interactions of the hypothalamic-pituitary-gonadal axis. But both PEG2 and PGF2 α can also be synthesized and released by astrocytes of the brain and thus, neuroglial interactions are involved in the phase release of the above mentioned hypothalamic releasing factor into the hypophyseal portal system influencing the massive release of luteinizing hormone and ovulation (disturbances of these processes in women can be one of the triggers for the development of early manifestations of rosacea).

However, under certain conditions various skin cells (Merkel cells, macrophages and others) are also capable of producing regulatory biologically active compounds identical to those in the endocrine system and participating in the metabolism of certain hormones, while they also express receptors for them providing auto- and paracrine (local) interactions, which is of clinical importance since manifestations of rosacea are rarely accompanied by severe disorders of the whole body. At the same time, the true hormonal role (with the development of endocrine effects) of biologically active substances synthesized in the skin (including prostaglandins) is possible in those parts of the dermis supplied with an extensive network of blood vessels. The synthesis of prostaglandins by keratinocytes of the epidermis of the facial skin in rosacea can also be induced by the immunosuppressive effect of the ultraviolet radiation, a frequent provoking factor of this dermatosis. As a result, the sensory reception in the corresponding area of the skin can change, which may lead to the reaction of the vessels in the dermis and metabolic transformations of prohormones or hormones with starting not only auto- and paracrine, but also neurocrine mechanisms, as well as systemic endocrine effects of molecules synthesized by skin cells [10].

With regard to the causes of rosacea flushing in women distinct biorhythms in the formation and secretion of sex hormones (depending on the age and physiological cycles – for example, “menstrual” biorhythm, “pregnancy-childbirth” biorhythm) and other hormones are also important [11], as well as functional changes in their activity: short-term / physiological (in cases where a temporary change of a function is necessary) or long-term and even permanent / pathological (when not only the function is disturbed, but also the structure of the hormone-producing unit which leads to hormonal disharmony, often of an integrated nature).

In this regard, special attention should be paid to the fact that in many women in the premenstrual period the vessels of the centers of the brain (hemodynamics) become the first “target” (also for prostaglandins). And, taking into account the fact that rosacea develops more often in older women (period of endocrine restructuring), this type of response includes not only sex hormones, but also an increase in the functional activity of the sympathoadrenal system, which is accompanied by additional manifestations of vegetative-vascular dysfunction in the form of flushing (in the head), fever, spotted hyperemia of the facial skin. At the same time, flushing in rosacea differs from flushing associated with climax through the absence of chills, persistent blood pressure fluctuations, tachycardia, and there is practically no headache. Flushing in rosacea also differs from flushing during migraine attacks, which is characterized by increased emotional lability, sleep disturbances, facial redness even before the onset of flushing itself, and the cause of which is often a congenital insufficiency of endogenous opioids and monoamine metabolism in human brain.

In respect to the problem of rosacea flushing considered in this work, it is important that of the 4 main groups of “non-hormonal” (in the direct meaning of this term) biologically active compounds of humoral

regulation which can be involved in the pathogenesis of this condition except for the so-called "paracrine signals" (norepinephrine, acetylcholine, and gamma-aminobutyric acid released from endings), "autocrine signals" (bradykinin and other biomolecules released during inflammation), "peptides", also "metabolites" – arachidonic acid derivatives (prostaglandins and other eicosanoids), a part of cell membranes, play a very important role.

When certain functions change, the mechanisms of maximum activity (homeokinetic), as well as homeostasis, aimed at restoring function, are activated. Both homeostatic and homeokinetic processes involve these metabolites (arachidonic acid – prostaglandins) belonging to so-called "simple" regulators (evolutionarily more ancient), but at the same time their complexes (both on external and internal membranes) are able to influence functional and structural cell formations [12].

For pathophysiological mechanisms of the development of flushing in rosacea it may be important that prostaglandins (in individual synapses) have been recently included (presumably) in one of the 5 groups of neurotransmitters of the central nervous system (including about 30 different biologically active compounds). In this case, we are talking about so-called "metabotropic" mediators having a postsynaptic effect through the activation of specific membrane enzymes. They are released together with the main ("ionotropic" mediator) and in the membrane itself (more often in the cytosol) they activate the second mediators thereby triggering a cascade of enzymatic reactions [12].

In the study of rosacea, very few attention is paid to the fact that in the above mentioned mechanisms the factors of primary ("vital") importance "work" the first. They include the need for sex hormones as a "vital" motivation for procreation [7]. It is evolutionarily programmed (reproductive function) and therefore any signals about structural and / or functional disorders in systems that ensure its proper functioning (satisfaction of the need) are primarily analyzed in the corresponding "centers" at different levels of the hierarchy of control in the subcortical and cortical regions of the brain. Since the onset of such disorders is often observed in "critical" moments of a woman's life (menstruation, pregnancy-childbirth, extinction of sexual function), they become one of the most frequent triggering mechanisms for the development of rosacea (including the stage of pre-rosacea with clinical manifestations of flushing). In this case, the main divisions of the nerve centers regulating the functions of the vessels are the first to react. They are located in the medulla oblongata, but it is not possible to accurately localize the isolated hemodynamic center (the so-called "vascular center") since in the body as a whole, a multilevel complex of neural structures is involved in it, which begins with nerve receptors of the vessels themselves and further includes the spinal, bulbar and higher located structures up to the cerebral cortex. The "vascular center" reacts to changes in the proportional ratio of hormones and metabolites secreted to the blood by the ovaries (with an increase in the specific gravity of prostaglandins) by widening its own vessels (the effect of prostaglandins is 100 times stronger than that of histamine). It has been experimentally proven that in the hypothalamus (in limbic structures as well as in the cortex) there are separate areas, upon irritation of which, isolated (!) impacts on hemodynamic control can be obtained. Such changes in hemodynamic parameters in the microvasculature of the facial skin during flushing in rosacea involve primarily the local blood flow system, which is initially aimed at increasing the blood supply to this area. And since it occurs on a small area, it does not affect the general hemodynamics (unlike flushing in "menopause" or "migraine").

Thus, prostaglandins act as modulators of the development of flushing in rosacea: on the one hand – as a powerful "vasodilator" (prostaglandin E₂), on the other – as "non-steroidal ovarian hormone", produced by ovaries in increased quantities. In addition, prostaglandins have a modulatory influence on the activity of ganglion neurons of the autonomic nervous system.

Taking into consideration the indicated complexity of the mechanisms of development of rosacea, the approach to the choice of treatment of the patients should be strictly individual and pathogenetically reasoned.

CONCLUSIONS

All 52 women with rosacea had in their history episodes of facial flushing accompanied by redness of its separate areas and local, moderate subjective sensations (heat, warmth). It allows to refer this manifestation to the obligatory and earliest signs of this dermatosis. The revealed increase in the levels of prostaglandins E₂

and F2 α in the blood serum of rosacea patients indicates their complex effect (as a pro-inflammatory factor and modulator of vasomotor reactions occurring in the microvasculature of the facial skin, and central regulatory structures of hemodynamics not accompanied by visible general body disorders), which must be taken into account in the treatment of patients.

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