

Avaliação Psicológica em Doentes com Rosácea: Um Estudo de Caso-Controlo com Symptom Checklist -90 - Revised

Rui Tavares-Bello¹, Nuno Torres²

¹Dermatology Service, Hospital Militar de Belém. Presently, Unidade de Dermatologia do Hospital dos Lusíadas, Lisboa, Portugal

²Clinical Psychologist, Doctorate in the Centre for Psychoanalytic Studies, University of Essex, UK. Presently, William James Center for Research, Instituto Superior de Psicologia Aplicada (ISPA), Lisboa, Portugal

RESUMO – Introdução: A rosácea, uma prevalente dermatose facial crónica, é classicamente considerada uma “psicodermatose” já que factores psicológicos são determinantes no seu desencadeamento ou evolução. Os doentes padecendo de rosácea foram descritos como imaturos, ansiosos, com reduzida auto-estima, com sentimentos de vergonha ou culpa, ou como “psiconeuróticos”, com configurações históricas ou obsessivo-compulsivas. **Objectivo:** Neste estudo foi investigado o distress psicopatológico de doentes com rosácea, comparados com um grupo de dermatopatas sofrendo de dermatoses agudas, acidentais, não conspícuas. Um objectivo adicional foi o de avaliar a influência determinada pelos dados demográficos e características clínicas sobre os resultados finais. **Material e Métodos:** Os participantes foram 53 doentes com rosácea e 190 outros dermatopatas, com idades compreendidas entre os 18 e os 72 anos foram recrutados numa consulta externa hospitalar de Dermatologia. A rosácea foi clinicamente avaliada e classificada bem como registada a duração da doença. Foi aplicado a todos os doentes o questionário de auto-resposta SCL-90-R para avaliar o distress psicológico e registar as queixas emocionais e psico-vegetativas. **Resultados:** As análises estatísticas revelaram uma efectiva influência independente das variáveis rosácea, género, nível escolar/educacional e da Interação rosácea/género nas variáveis psicométricas. Os doentes com Rosácea revelaram valores superiores aos da população do grupo controlo nas dimensões sensibilidade interpessoal ($F[1,241]=3,57, p<0,01$). No que concerne às diferenças entre géneros, as doentes com rosácea registaram valores superiores aos dos da população controlo nas dimensões ansiedade, depressão, sensibilidade interpessoal, obsessões e compulsões, ideação paranóide e somatização, ao contrário dos doentes do género masculino em que tal apenas se verificou na sensibilidade interpessoal. No que se refere aos efeitos da duração da doença, os doentes com rosácea com mais de 1 ano de duração registaram scores significativamente mais elevados de ideação paranóide do que os doentes com durações de doença inferiores a um ano ($F[2,52]=3,79, p<0,05$). **Conclusões:** Os doentes sofrendo de rosácea – em contraste com outros doentes com outras dermatoses – revelam um distress psicossocial significativo, o qual não se correlaciona no entanto com o sub-tipo clínico da dermatose.

PALAVRAS-CHAVE – Psicometria; Rosácea/psicologia; Stress Psicológico.

Psychological Evaluation in Rosacea Patients: A Case-Control Study using Symptom Checklist -90 - Revised

ABSTRACT – Background: Rosacea, a prevalent chronic facial skin condition, is classically referred to as a “psychodermatosis”, in that psychological factors are relevant both in its initiation and course. Rosacea patients have been described as immature, anxious, with diminished self-esteem and with feelings of guilt and shame, or as psychoneurotic, with hysterical or obsessive compulsive configurations. **Objective:** In this study we investigated the psychopathological distress experienced by rosacea patients, as compared to a group of dermatological patients suffering from acute, non-conspicuous, accidental dermatoses. One additional purpose was to assess the influence that demographic features and clinical factors had on final results. **Patients/Methods:** A total of 243 patients with rosacea, aged from 18 to 72 years’ old were enrolled from an outpatient dermatology clinic in a hospital setting. Rosacea was objectively rated and disease duration recorded. The SCL-90 (R) was used to assess participants psychological distress and to record

Correspondência: Rui Carlos Tavares-Bello, MD
Av. António Augusto Aguiar, 24 – 8º Dto
1050-016 Lisboa, Portugal
E-mail: dermoclinica@netcabo.pt

Recebido/Received
29 Janeiro/29 January 2016
Aceite/Accepted
1 Abril/1 April 2016

Artigo Original

emotional and psycho vegetative complaints. **Results:** Statistical analysis revealed a definite independent influence of the variables rosacea, gender, school level, and also of the interaction rosacea/gender on the psychometrical variables. Rosacea patients scored higher than controls with respect to interpersonal sensitivity ($F[1,241]=3.57, p<0.01$). Concerning gender differences, female patients scored always higher than controls in anxiety, depression, interpersonal sensitivity, obsession-compulsion, paranoid ideation and somatization, whereas male patients did so only for interpersonal sensitivity. As to the effects of disease duration, rosacea patients' for more than one year revealed significantly higher scores of paranoid ideation than patients' with less than one year duration ($F[2,52]=3.79, p<0.05$). **Conclusions:** Patients suffering from rosacea – as opposed to other dermatoses – do experience significant psychosocial distress, which was nevertheless found to be unrelated to disease clinical sub-type.

KEY-WORDS – Psychometrics; Rosacea/psychology; Psychometrics; Stress, Psychological.

INTRODUCTION

Rosacea is a prevalent chronic inflammatory skin disorder that involves primarily the convex areas of the face. Often called "the curse of the Celts", rosacea in fact is more common, though not exclusive, in fair-skinned people and in women, although men seem to be more severely affected. The onset is usually in the 3rd or 4th decades of life and the peak incidence is around 40/50 years of age.¹⁻⁴

Several clinical signs and symptoms (facial flushing, persistent erythema, telangiectasia, papules, pustules, tissue hypertrophy, ocular complaints and skin sensitivity...) do occur in several combinations and grades of severity although in the majority of patients a particular presentation usually dominates the clinical appearance.⁵ Accordingly, the condition has been classified on clinical grounds, into four major sub-types: 1) erythemato-telangiectatic; 2) papulo-pustular; 3) phymatous and 4) ocular rosacea⁴ (Fig.s 1-5).

Often both patients and non-dermatologist physicians underestimate the condition, taking it as a merely cosmetic concern or, otherwise, view it just as minor psychological ailment. In fact, blushing – the most peculiar and the most human of all expressions⁶ – has been usually regarded as a hallmark of



Figure 2 - Erythemato-telangiectatic rosacea.



Figure 1 - Erythemato-telangiectatic rosacea.



Figure 3 - Papulo-pustular rosacea.

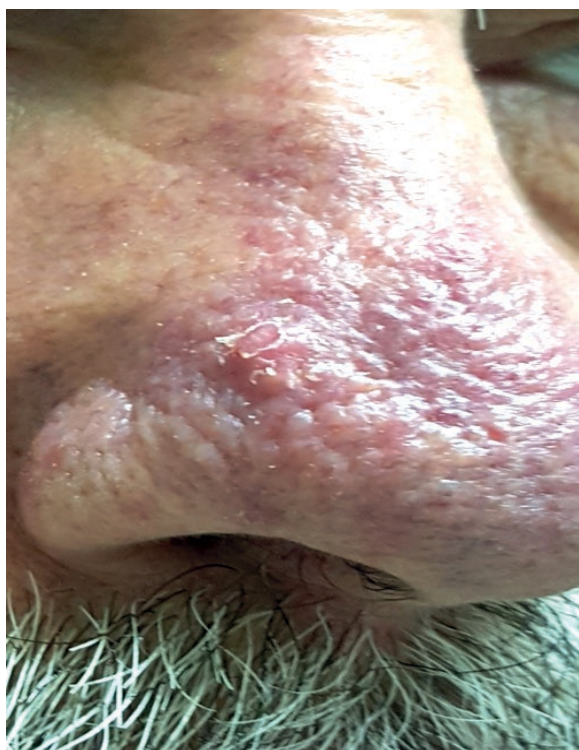


Figure 4 - Phymatous rosacea.

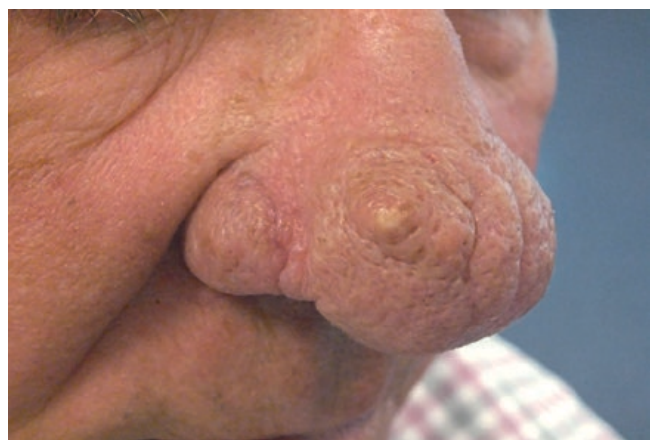


Figure 5 - Phymatous rosacea.

embarrassment,⁷ but the red face with hypertrophied nose is also viewed as a sign of excessive alcohol consumption.⁵ Moreover, the disorder conveys patients a disgraceful appearance, which, along with the resulting sense of shame and social inadequacy portend important repercussion in their daily lives.⁸

Psychological factors are relevant both in the initiation and course of rosacea. In fact, for the last century, both social and emotional impact, diminished self-esteem and psychiatric comorbidities have been reported to occur in these patients.⁹⁻¹² They have been described as immature, anxious, with diminished self-esteem and feelings of guilt and shame,^{13,14} or as

psychoneurotic, with hysterical or obsessive-compulsive configurations.¹⁵

In the present study we intended to explore and draw conclusions on the psychopathologic distress experienced by Portuguese rosacea patients as compared to a group of dermatological patients suffering from acute, non-conspicuous, accidental dermatoses.

METHODS

Sample/Population: Were enrolled 53 rosacea (ROS) patients from an outpatient dermatology clinic in a public hospital setting, in Lisbon. Their ages ranged from 18 to 72 years old (mean age was 35.8 years and standard deviation of 16.1 years). A control group with 190 patients were also included, that suffered from acute, accidental, non-conspicuous dermatoses (as opposed to long lasting, constitutional dermatoses or those that affect normally exposed parts of the skin like the face, hands or the neck area or otherwise areas with important psychological impact such as the hands or genitalia). Examples of those that were included in the control group: tinea versicolor, tinea pedis, superficial bacterial, fungal and viral infections, contact dermatitis, toenail dystrophies, pityriasis rosea, mild scalp seborrheic dermatitis...).

Procedure: Participants were randomly picked from our Clinical nosological database and asked to participate in the study. Demographic features (gender, age, marital status and educational level) and clinical data (disease duration and clinical classification) were controlled. Of the 53 ROS patients, the subtypes erythemato-telangiectatic and papulopustular variants clearly predominated, with 20 and 25 patients, respectively. The phymatous variant was present only in 8 cases. Ocular rosacea was diagnosed in 10 patients, but never an isolated finding and, therefore, it was not considered as a distinct subgroup for analysis.

Instrument: The measuring tool was the Symptom Checklist - 90 (R) (SCL-90 (R)),¹⁶ namely the Portuguese version.¹⁷ SCL-90 (R) is a multidimensional self-report symptom inventory designed to evaluate psychological distress and to record emotional and psychovegetative complaints. Its relevance has been proven in psychiatric and nonpsychiatric patients as well as in normal, non-emotionally disturbed individuals. It is a 90-item questionnaire that includes the following 9 subscales: *somatization* (12 items); *obsessive-compulsive* (10 items); *interpersonal sensitivity* (9 items); *depression* (13 items); *anxiety* (10 items); *anger/hostility* (6 items); *phobic anxiety* (7 items); *paranoid ideation* (6 items) and *psychoticism* (10 items). Subjects respond to each of the 90 statements on a five-point Likert scale, ranging from "not at all" (scored as 0) to "extremely" (scored 4). The final score of each subscale is the mean of the corresponding subscale items.

Statistical analyses were performed by the program SPSS version 11.0. Demographic differences were analysed by One-Way Analysis of variance (ANOVA); all the other analyses with categorical independent variables were performed using Multivariate Analysis of Covariance (Mancova); the analyses with ordinal independent variables were performed using Spearman's non-parametric correlation methods.

Artigo Original

RESULTS

Age differences were not significant ($F [1, 241] = 3.18, p = 0.08$) between the rosacea group ($M = 35.6, SD = 16.1$) and the control group ($M = 30.8, SD = 18.5$). The same does not apply however to the other demographic variables, with women overrepresented ($F [1, 241] = 9.16, p = 0.003$) in the study group (64%) and underrepresented in the control group (41%), and also with a significant difference found between the 2 groups in the variable educational level ($F [1, 241] = 14.48, p < 0.001$), with ROS patients having higher school level ($M = 12.5, SD = 3.9$) than controls ($M = 10.3, SD = 3.6$). Multivariate analyses of covariance (ROS and gender as independent and SCL-90® subscales as dependent variables) were performed. Pillai's and Wilks' Lambda tests allowed to see that there were significant effects of the independent variables in the psychometric variables (Table 1).

Univariate effects tests failed to demonstrate significant differences in the psychometric variables between the rosacea and control patients, except for *interpersonal sensitivity*. In fact, ROS patients scored significantly higher than controls in this sub scale (Table 2). As far as gender is concerned, no significant difference could be found between males and females in the SCL-90® scores, except for a marginally significant ($F [1, 238] = 3.29, P = 0.07$), higher depression score in males ($M = 0.87, SD = 0.67$), as compared to females ($F = 0.84, SD = 0.61$).

Significant two-way interaction effects between gender and rosacea were however found in the sub scales *anxiety* ($F [1, 238] = 4.77, p = 0.03$), *depression* ($F [1, 238] = 8.97, p = 0.003$), *interpersonal sensitivity* ($F [1, 238] = 5.25, p = 0.02$), *obsessive-compulsive* ($F [1, 238] = 13.64, p < 0.001$), *paranoid*

Table 1 - Effects of Rosacea, gender, Educational level and of Interaction between Rosacea and Gender on SCL-90 scale scores, using "Mancova Multivariate Test".

Effect	Pillai's Trace F	Sig.	Observed Power
Rosacea	4.002	0.000	0.995
Gender	2.077	0.033	0.863
Rosacea* Gender	1.984	0.042	0.844
School level	4.312	0.000	0.997

ideation ($F [1, 238] = 5.19, p = 0.02$) and, lastly, *somatization* ($F [1, 238] = 9.89, p = 0.002$).

These interaction effects showed that female ROS patients scored higher than males, as opposed to the control group, where males clearly outscored females. It was also clear that while female ROS patients scored always higher than female controls, the very opposite was seen in the male population who, except for *interpersonal sensitivity*, scored always lower than their male counterpart controls.

Clinical classification, gender and psychometric variables, using both a One-Way Analysis of variance between gender and clinical sub-types ($F [1, 52] = 0.66, p = 0.42$) and Spearman's non-parametric correlations between clinical sub-types and the psychometric variables, both failed to show

Table 2 - SCL-90 scores of rosacea and control patients

		Mean	St error	Significance
ANXIETY	0-Control	0.86	0.05	
	1-Rosacea	0.83	0.09	
DEPRESSION	0-Control	0.88	0.05	
	1-Rosacea	0.77	0.09	
PHOBIC ANXIETY	0-Control	0.49	0.04	
	1-Rosacea	0.49	0.08	
HOSTILITY	0-Control	0.88	0.05	
	1-Rosacea	0.91	0.10	
INTERPERSONAL SENSITIVITY	0-Control	0.82	0.05	**
	1-Rosacea	1.10	0.09	
OBSESSIVE-COMPULSIVE	0-Control	1.07	0.05	
	1-Rosacea	1.02	0.09	
PARANOID IDEATION	0-Control	0.88	0.05	
	1-Rosacea	0.99	0.09	
PSYCHOTICISM	0-Control	0.56	0.04	
	1-Rosacea	0.57	0.08	
SOMATIZATION	0-Control	0.82	0.04	
	1-Rosacea	0.79	0.08	

** $P < 0.01$

Table 3 - Effects of age, rosacea’s duration, gender and of interaction between rosacea’s duration and gender on SCL-90 scale scores using “Mancova Multivariate Test”.

Effect	Pillai’s Trace F	Sig.	Observed Power
Age	4.26	0.00	0.99
Duration	1.13	0.34	0.71
Gender	1.87	0.09	0.73
Duration X Gender	0.53	0.94	0.33

significant differences (Table 3). Concerning disease duration, a multivariate analysis of covariance was performed with the SCL-90® subscales as dependent variables, disease duration

(3 levels: <1Y; 1-5Y and >5Y) and gender as independent ones and age as co-variable. No effects reached the level of significance. However, univariate tests revealed significance ($F[2,52]=3.79, p=0.03$) of disease duration in *paranoid ideation* (Table 4), where scores were shown to be much higher in patients suffering from the condition for more than one year and slightly decreasing in the longer lasting disease (>5Y), particularly among males (Fig. 6).

DISCUSSION

The precise elucidation on the exact aetiology of rosacea (ROS) is yet to be made. Although successively attributed to genetic, behavioural, psychogenic, climatic, nutritional, infectious and immunological factors,¹⁸⁻²¹ evidence has accumulated that underneath the diverse clinical settings, there are always vascular abnormalities, as such strengthening Unna’s original view point of rosacea being basically a vascular disorder.^{22,23} In fact, a basic microcirculatory disturbance of the facial angular veins (involved in a direct brain cooling mechanism)^{23,24} has been said to play a pivotal role. Additionally,

Table 4 - SCL-90 scores according to disease’s duration¹

Dependent Variable	Duration	Mean	Std. Deviation	Significance
ANXIETY	1.00	0.60	0.45	
	2.00	0.97	0.51	
	3.00	0.75	0.46	
DEPRESS	1.00	0.42	0.46	
	2.00	0.90	0.70	
	3.00	0.74	0.56	
FOBANXI	1.00	0.26	0.28	
	2.00	0.53	0.54	
	3.00	0.52	0.58	
HOSTILIT	1.00	0.58	0.49	
	2.00	1.16	0.83	
	3.00	0.75	0.56	
INTSENSE	1.00	0.76	0.24	
	2.00	1.23	0.64	
	3.00	1.06	0.63	
OBCOMP	1.00	0.60	0.46	
	2.00	1.07	0.67	
	3.00	1.08	0.60	
PARANIDE	1.00	0.64	0.32	*
	2.00	1.16	0.48	
	3.00	0.91	0.48	
PSYCHOTI	1.00	0.47	0.44	
	2.00	0.65	0.43	
	3.00	0.51	0.48	
SOMATIZA	1.00	0.57	0.53	
	2.00	0.92	0.58	
	3.00	0.73	0.47	

*** P<=0.05**

¹ three levels scored as: 1-less than one year; 2-one to five years and 3-more than five years

Artigo Original

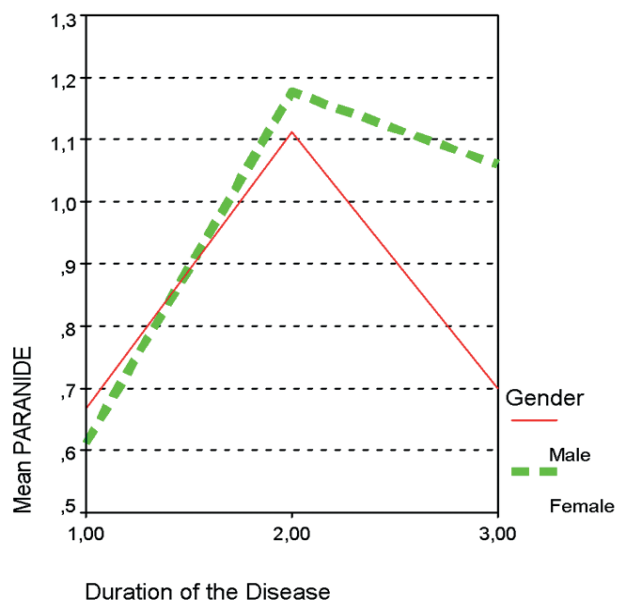


Figure 6 - Means of paranoid ideation in three stages of rosacea's duration and by gender; Three levels scored as: 1- less than one year; 2- one to five years and; 3 - more than five years.

association with migraine and with vasodilator substances (alcohol, foods...) ²⁵⁻²⁸ and life circumstances (menopause...) are frequently observed in clinical practice. On investigative grounds, it has been shown that the potent vasodilator substance P is increased in the serum and it is over expressed in the perivascular neural network of the affected skin. ^{29,30} Other neural peptides - VIP and CRH - are probably involved as well in the neural vasodilatory and pro inflammatory background of rosacea. ³¹⁻³³ In short, it is believed that whatever the nature of the stimulus - emotional, environmental, microbiological, immunological... - frequent and repeated blushing may lead, on the long term, to a permanent loss of the skin vascular tone, as such resulting in erythema and oedema of the tissues, ³⁴ further aggravated by actinic damage of the dermal connective tissue and the ensuing loss of supportive strength to the vasculature walls. ³⁵

The way these classic and new pathogenic data (namely on the role of the disturbed innate immunity and systemic cardiovascular comorbidities) ³⁶⁻³⁹ relate with the clinical evidence on rosacea patients' personality and psychism is a matter still under debate and investigation. The fact remains that ROS patients are usually said to be anxious or phobic, with obsessive traits or disorder and, accordingly, their lives are compromised by self-consciousness, social anxiety and avoidance. ^{17, 40}

The present study is a hospital-based comparative one, encompassing 53 adult rosacea patients and 190 control subjects with other skin diseases. The operational tool was the SCL-90®, a widely used multidimensional self-report inventory, designed to detect and quantify different aspects of psychopathology. Statistical analysis allowed detecting definite effects of the variables rosacea, gender, educational level and the

interaction rosacea/gender in the psychometric dependent variables (SCL-90® subscales). Overall, the ROS group of patients scored significantly higher than controls with respect to *interpersonal sensitivity*, a dimension that normally denotes feelings of personal inadequacy and inferiority, mixed with feelings of being criticized by others. However, when isolated and discriminated for gender and for the presence/absence of rosacea, data clearly demonstrated much higher scoring among ROS female patients as far as *anxiety*, *depression*, *interpersonal sensitivity*, *obsessive-compulsive*, *paranoid ideation* and *somatization*. The influence of gender was also evident in the fact that female ROS patients scored always higher than their control counterparts, in contrast with the ROS male patients that, somewhat surprisingly, - except for personal sensitivity - scored lower than the male controls. Also of note, the different clinical subtypes of ROS showed no significant difference in what concerns the effect on psychometric values.

Although still a small population and merely correlational data, these results do confirm those previously reported in that ROS, as well as chronic dermatologic disorders, portend serious psychological and social repercussions to the individual. ^{41,42} The psychometric sub scale *interpersonal sensitivity* clearly underlines that fact. Also noteworthy we found gender differences that underline - in a mostly urban, middle class population - the strong impact skin and looks have in females' self-image and esteem and social interactions. Bearing in mind the chronicity and visibility of rosacea, it is thus hypothetically conceivable that most patients gradually become self-conscious of their ailment, in an extent that may both interfere with social interactions and, as such, possibly reinforcing disease pathomechanisms via generated autonomic responses that may further increase facial erythema, ⁴³ skin inflammation and, possibly, systemic comorbidities. These complex chains of events would ultimately result on positive self-perpetuating feedback mechanisms that ultimately would result in an endless, vicious circle.

CONCLUSIONS

Definite effects were detected of the variables rosacea, gender, educational level and the interaction rosacea/gender in the psychometric variables. As a whole, the rosacea group scored significantly higher than controls with respect to *interpersonal sensitivity*, which denotes feelings of inferiority, personal inadequacy and of being criticized by others. This is particularly so in the female gender, with male patients seemingly somewhat more protected concerning these psychometric scale variables. Finally, it clearly deserves to be mentioned the lack of significance between ROS clinical subtype and *psychopathology*, as such underlining the subjective and individually based character of psychological suffering in this setting.

Surely deserving further investigation, it is our goal to extend this sample in order to both further investigate these trends and explore these demographic correlations. One interesting approach would be to compare these data with those collected from other chronic facial dermatoses such as acne.

Notwithstanding, a complementary approach that may be interesting to explore would be to correlate these data with QoL measurements including both a specific rosacea (ROSAQoL)⁴⁴ and a specialist Quality of Life instrument (DLQI).

Conflitos de interesse: Os autores declaram não possuir conflitos de interesse. **Suporte financeiro:** O presente trabalho não foi suportado por nenhum subsídio ou bolsa. **Direito à privacidade e consentimento escrito:** Os autores declaram que pediram consentimento ao doente para usar as imagens no artigo.

Conflicts of interest: The authors have no conflicts of interest to declare. **Financing Support:** This work has not received any contribution, grant or scholarship. **Privacy policy and informed consent:** The authors declare that the patient gave written informed consent for the use of its photos in this article.

REFERENCES

- Plewig G, Kligman AM. Rosacea. In: Plewig G, Kligman AM, editors. Acne and Rosacea. Berlin: Springer Verlag; 2000. p.456-67.
- Berg M, Liden S. An epidemiological study of rosacea. *Acta Dermatol Venereol.* 1989; 69: 419-23.
- Drake L. Survey maps typical progression from rosacea's first appearance. *Rosacea Revi.* 1995;2.
- Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, et al. Standard classification of rosacea: Report of the national Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002; 46:584-7.
- Powell C: Rosacea. *N Engl J Med,* 2005; 352:793-803.
- Darwin C. The expression of the emotions in man and animals (1872). In: Porter DM, Graham PW, editors *New York: Penguin Books:* 1993.p. 364-93.
- Buss AH. *Self-consciousness and Social Anxiety.* San Francisco: Freeman; 1980.
- Drott C, Claes G, Olsson-Rex L, Dalman P, Fahlén T, Göthberg G. Successful treatment of facial blushing by endoscopic transthoracic sympathectomy. *Br J Dermatol.* 1998; 138:639-43.
- Sowinska-Gługiewicz I, Ratajczak-Stefanska V, Maleszka R. Role of psychological factors in course of the rosacea. *Rocz Akad Med Białymst.* 2005; 50Suppl 1:49-53.
- Klüber R, Wittkover E. The pathogenesis of rosacea. *Br J Dermatol Syphil.* 1939; 2: 501-19.
- Soby P. Aetiology and pathogenesis of rosacea. *Acta Dermatol Venereol,* 1950; 30:137-58.
- Balkrishnan R, McMichael AJ, Hu JY, Camacho FT, Shew KR, Bouloc A, et al. Correlates of health-related quality of life in women with severe facial blemishes. *Int J Dermatol.* 2006; 45:111-5.
- Gupta MA, Gupta AK, Chen SJ, Johnson AM. Comorbidity of rosacea and depression: an analysis of the National Ambulatory Medical Care Survey and National Hospital Ambulatory Care Survey-Outpatient Department data collected by the US National Center for Health Statistics from 1995 to 2002. *Br J Dermatol,* 2005; 153:1176-81.
- Cormia FE. Basic concepts in the production and management of the psychosomatic dermatoses-II. *Br J Dermatol.* 1951; 63:129-51.
- Panconesi E. Psychosomatic Dermatology. In: Panconesi E, editors. *Clinics in Dermatology Stress and Skin Diseases: Psychosomatic Dermatology.* Philadelphia: JB Lippincott; 1984.p.131-3.
- Derogatis LR, Lipman RS, Covi L. SCL-90: An Outpatient Psychiatric Rating Scale – Preliminary Report. *Psychopharmacol Bull.* 1973; 9:13-28.
- Baptista A. A génese da perturbação de pânico: A importância dos factores familiares e ambientais durante a infância e a adolescência. [Dissertação de doutoramento,]. Porto: Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto; 1993.
- Koblentz CS. Flushing reactions and rosacea. In: Koblentz CS, editor. *Psychocutaneous Disease.* Orlando: Grune and Stratton; 1987.p. 230-7.
- Grosshans E. Bilan des notions étiologiques actuelles de la rosacée. *J Agregés.* 1977; 10:427-33.
- Marks R. Concepts in the pathogenesis of rosacea. *Br J Dermatol.* 1968; 80:170-7.
- Rebora A. Rosacea. *J Invest Dermatol.* 1987; 88(Suppl 3):569-605.
- Wilkin JK. Rosacea: a review. *Int J Dermatol.* 1983; 22:393-400.
- Wilkin JK. Rosacea: pathophysiology and treatment. *Arch Dermatol.* 1984; 130:359-62.
- Brinell H, Friedel J, Caputa M, Cabanac M, Grosshans E. Rosacea: disturbed defense against brain overheating. *Arch Dermatol Res.* 1989; 281:66-72.
- Spoendlin J, Voegel JJ, Jick SS, Meier CR. Migraine, triptans, and the risk of developing rosacea. A population-based study within the United Kingdom. *J Am Acad Dermatol,* 2013; 69:399-406.
- Caputa M, Perrin G, Cabanac M. Ecoulement sanguine réversible dans la veine ophtalmique: mécanisme de refroidissement sélectif du cerveau humain. *CR Acad Sci.* 1978; 287:1011-4.
- Wilkin JK. Heat, not caffeine, induces flushing in erythematotelangiectatic rosacea. *J Invest Dermatol* 1979; 73:310-2.
- Wilkin JK. Quantitative assessment of alcohol-provoked flushing. *Arch Dermatol.* 1986; 122:63-5.
- Kurkmoglu N, Alaybeyi F. Substance P immunoreactivity in rosacea. *J Am Acad Dermatol.* 1991; 25:725-6.
- Powell FC, Corbally N, Powell D. Substance P and rosacea. *J Am Acad Dermatol.* 1993; 28:132-3.
- Wollina U. Rhinophyma-unusual expression of simple-type keratins and S 100 A in sebocytes and abundance of VIP-receptor-positive dermal cells. *Histol Histopathol.* 1996; 11:111-5.

Artigo Original

32. Fimmel S, Schnitger A, Glass E, Zouboulis CC. Keratinocyte- and sebocyte-derived factors modify UVB activity on endothelial cells: a possible mechanism for the development of vascular changes in rosacea. *J Invest Dermatol Res.* 2004; 122:A3.
33. Zouboulis CC. Acne vulgaris and rosacea. *In: Grans-tein RD, Luger T, editor. Neuroimmunology of the Skin. Basic Science to Clinical Practice. Berlin: Springer-Verlag; 2009. p. 225-32.*
34. Wilkin JK, Josephs JA. Infrared photographic studies of rosacea. *Arch Dermatol.* 1980; 116:676-8.
35. Marks R, Harcourt-Webster JN. Histopathology of rosacea. *Arch Dermatol.* 1969; 100:683-91.
36. Yamasaki K, Di Nardo A, Bardan A, Murakami M, Ohtake T, Coda A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007; 13:975-80.
37. Bevins CL, Liu FT. Rosacea: skin innate immunity gone awry? *Nat Med.* 2007; 13:904-6.
38. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case-control study. *J Eur Acad Dermatol Venereol.* 2014; 28:1165-9.
39. Hua TC, Chung PI, Chen YJ, Wu LC, Chen YD, Hwang CY, et al. Cardiovascular comorbidities in patients with rosacea: A nationwide case-control study from Taiwan. *J Am Acad Dermatol.* 2015; 73:249-53.
40. Cotterill JA. Rosácea y enrojecimiento facial, hiperhidrosis. *In: Grimalt F, Cotterill JA, editors. Dermatología y Psiquiatria – Historias Clínicas Comentadas. Madrid: Biblioteca Aula Medica; 2002. p. 239-44.*
41. Finlay AY, Ryan TJ. Disability and handicap in dermatology. *Int J Dermatol.* 1996; 35:305-11.
42. Jowett S, Ryan T. Skin disease and handicap: An analysis of the impact of skin conditions. *Soc Sci Med.* 1985; 20:425-9.
43. Bar LH, Kuypers BR. Behaviour therapy in dermatologic practice. *Br J Dermatol.* 1973; 88:591-8.
44. Nicholson K, Abramova L, Chren MM, Yeung J, Chon SY, Chen SC. A pilot quality-of-life instrument for acne rosacea. *J Am Acad Dermatol.* 2007; 57:213-21.