

Original Research Article

Study of serum angiotensin converting enzyme levels in pemphigus vulgaris

V. Anand Kumar, J. Vijaya Shree*

Department of Dermatology, Venereology and Leprosy, Great Eastern Medical School and Hospital, Srikakulam, Ragolu, Andhra Pradesh, India

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***Correspondence:**

Dr. J. Vijaya Shree,

E-mail: dr.j.vijayashree@gmail.com

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ABSTRACT

Background: This study aimed to evaluate the serum angiotensin converting enzyme (ACE) levels in patients with pemphigus vulgaris compared with healthy volunteers.

Methods: In this study, 40 patients were selected in the study group with pemphigus vulgaris and 40 patients were selected in the control group i.e. healthy group. Serum ACE levels were determined by spectrophotometric method.

Results: The mean ACE levels in study group and control group were 26.98 ± 15.87 and 32.57 ± 20.98 respectively. There was no statistically significant difference between both the groups ($p=0.11$). The mean ACE levels were 26.25 ± 12.36 and 26.14 ± 13.89 in females and males respectively in the study group which showed no significant difference ($p=0.95$). In the control group, the mean ACE levels were 26.22 ± 19.77 and 38.54 ± 11.11 in females and males respectively which showed a statistically significant difference ($p=0.04$). The mean ACE levels were higher in healthy males when compared to the males in the study group. The mean serum levels in females of both the groups were almost same.

Conclusions: The serum ACE level was considerably lower in male study group i.e. pemphigus vulgaris patients compared with male control group i.e. healthy group, despite lack of any significant difference of serum ACE level between pemphigus and control group. Hence, ACE might have some relation with pemphigus vulgaris especially in male patients.

Keywords: Pemphigus, Desmoglein

INTRODUCTION

Pemphigus vulgaris is an autoimmune, life threatening, intraepidermal blistering disease, clinically characterized by cutaneous and/or mucosal blisters and erosions. It is mediated by circulating IgG antibodies directed against keratinocyte cell surface molecules desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1).¹ Interaction between the antibody and the desmoglein may have a direct effect on desmosomal adherens and also may trigger a cellular process that results in acantholysis. The disease can develop spontaneously in majority of patients (Idiopathic

or due to certain medication (Drug induced pemphigus).² Some drugs induce antibody formation, which results in acantholysis similar to idiopathic pemphigus but other drugs induce acantholysis directly in the absence of antibody formation. Drugs that induce pemphigus may be categorized into 2 groups: thiol drugs and nonthiol drugs. Penicillamine, captopril, and enalapril are the thiol drugs most often associated with drug-induced pemphigus. This study was performed with the hypothesis that serum ACE levels might alter in pemphigus patients as ACE inhibitors will cause the pemphigus in some individuals. Hence, this study is aimed to evaluate the serum ACE

levels in patients with pemphigus vulgaris compared with healthy volunteers.

METHODS

This study was conducted in Department of Dermatology, venereology and leprosy from November 2015 to October 2017. At the time of enrolment, informed consent was obtained from all the patients involved in the study. Institutional ethical committee clearance was obtained. This study included 40 patients who were older than 20 years, with pemphigus vulgaris. Pemphigus was diagnosed clinically, confirmed by histopathologically and immunofluorescence findings. Exclusion criteria were patients who had diabetes mellitus, hypertension, hyperthyroidism, sarcoidosis and those patients who had positive history of ACE inhibitors consumption. The control group consisted 40 clinical staff with no past medical history for intake of corticosteroids. Those who were under treatment of systemic corticosteroids at least 3 weeks before the study in the control group were excluded, and those who had the same age and sex as the study group were selected. The exclusion criteria were same as the study group. The serum ACE levels were determined by using 10 cc venous blood of each participant. The coagulated blood samples were centrifuged to separate serum and serum was collected. The sera were stored at -20°C, and then the samples were sent to laboratory for measuring the serum ACE levels. Serum ACE levels were measured by spectrophotometric method. For more than 14 years of age, the normal ACE reference range level was 8-65 units. Questionnaires were filled by physician regarding the patients duration of disease, family history of pemphigus vulgaris, sites of involvement of pemphigus vulgaris, past medical history, history of their medications. The severity of the disease was detected by pemphigus area and activity score (PAAS). It is an integer scale which is sum of mucous membrane and cutaneous score. Results were expressed in mean \pm standard deviation. Samples t-tests were used to compare the mean of continuous variables.

RESULTS

In this study, 40 patients were selected in the study group with pemphigus vulgaris and 40 healthy individuals were selected in the control group.

Table 1: Demographic distribution in the study.

Sex distribution	Study group	Control group
Males	18 (45%)	17 (42.5%)
Females	22 (55%)	23 (57.5%)
Mean age (mean\pmSD)	45.23 \pm 9.87 years	45.01 \pm 2.44

Table 1 shows that in the study group, males were 18 (45%), females were 22 (55%); in the control group, males were 17 (42.5%), females were 23 (57.5%). Mean Age of study group was 45.23 \pm 9.87 years, mean age of

control group was 45.01 \pm 2.44 years. The median duration of the disease was 5 months (10.69 \pm 1.57 months).

Table 2: Clinical severity assessment of pemphigus vulgaris patients.

Severity assessment	Study group (%)
Affected mucous membranes and skin	20 (50)
Only mucous membrane involvement	12 (30)
Only skin involvement	8 (20)

Table 2 shows that after severity assessment, pemphigus affected both mucous membrane and skin in 20 (50%) of patients, pemphigus affected only mucous membrane in 12 (30%) of patients, pemphigus affects only skin in 8 (20%) of patients. Among the 32 patients with mucous membrane and mucocutaneous involvement pemphigus vulgaris, oral mucosa lesions were observed in 100% i.e. 32 patients, nasal mucosal lesions were observed in 3 patients, genital mucosal lesions were observed in 1 patients and conjunctival mucosal lesions were observed in 4 patients.

Table 3: Based on physician's global assessment and PAAS in patients with pemphigus.

	Number (%)
Physician's global assessment	
Mild	22 (55%)
Moderate	15 (37.5%)
Severe	3 (7.5%)
PAAS (median)	
Females (n=22)	2.8
Males (n=18)	3
Total (n=40)	3

Table 3 shows that on physician's global assessment, mild were 22 (55%), moderate were 15 (37.5%) and severe were 3 (7.5%). PAAS was 2.8 in females and it was 3 in males.

Table 4: Mean \pm SD of serum converting enzyme level in both groups.

Laboratory findings		
Groups	Study group (n=40)	Control group (n=40)
Serum ACE level	26.98 \pm 15.87	32.57 \pm 20.98
Females	25.25 \pm 12.36	26.22 \pm 19.77
Males	26.14 \pm 13.89	38.54 \pm 11.11
Types of pemphigus vulgaris		
Cutaneous (n=8)	36.08 \pm 9.01	---
Mucosal (n=12)	17.25 \pm 1.47	---
Mucocutaneous (n=20)	24.87 \pm 3.22	---

Table 4 shows that the mean ACE levels in study group and control group were 26.98 ± 15.87 and 32.57 ± 20.98 respectively. There was no statistically significant difference between both the groups ($p=0.11$). The mean ACE levels were 26.25 ± 12.36 and 26.14 ± 13.89 in females and males respectively in the study group which showed no significant difference ($p=0.95$). In the control group, the mean ACE levels were 26.22 ± 19.77 and 38.54 ± 11.11 in females and males respectively which showed a statistically significant difference ($p=0.04$). The mean ACE levels were higher in healthy males when compared to the males in the study group. The mean serum levels in female of both the groups were almost same. The cutaneous type of pemphigus showed higher mean ACE levels when compared to other two types of pemphigus. There was no significant difference between the three types of pemphigus vulgaris i.e. ACE of mucocutaneous and cutaneous cases ($p=0.13$), and mucocutaneous and mucosal patients was $p=0.50$.

DISCUSSION

Pemphigus vulgaris is an autoimmune disease which involves skin and mucous membranes causing painful blisters. It is the most common type of autoimmune blistering disorders. Thiol drugs such as penicillamine and captopril have been studied very well; however, non-thiol drugs, including other ACE inhibitors can be the causative agent of pemphigus.³⁻⁵ According to recent findings, angiotensin converting enzyme (ACE) modulates cutaneous inflammation. Angiotensin converting enzyme is a zinc based metalloprotease. The enzyme is non-specific and it has two major roles, one is to regulate local renin-angiotensin system with the generation of angiotensin II from angiotensin I and another one is conversion of substance P-inducing bradykinin to inactive molecules. Many inflammatory responses like plasma extravasation, leukocyte activation, endothelial cell adhesion molecule expression, cytokine production, and mast cell activation can be induced by Substance P, whereas, bradykinin (BK) is a powerful mediator capable of augmenting symptoms of inflammation, including vasodilation, plasma extravasation, and pain by activating bradykinin receptors (B-R), in particular the B2-R. Activation of B2-R on sensory nerves triggers the release of neuropeptides such as Substance P which results in the amplification of neurogenic inflammation. The biological functions of these neuropeptide mediators are terminated by proteolytic enzymes such as the zinc metalloprotease angiotensin-converting enzyme (ACE) so ACE plays an important role in regulating neurogenic inflammation.^{6,7}

Little is known about a possible contribution of ACE in the pathogenesis of skin diseases, though there are studies evaluating the serum ACE level in dermatoses such as psoriasis and lichen planus. Huskic et al conducted a study in which 60 patients with psoriasis and in 16 healthy individuals were compared. The patients were divided into three groups: psoriasis with solitary

lesions ($n=20$), psoriasis with multiple disseminated lesions ($n=20$) and erythrodermic psoriasis ($n=20$). Before and after therapy, the serum ACE activity was determined. Serum ACE activity was significantly increased in patients with psoriasis (47.20 ± 2.06 U/L) before therapy in comparison to healthy individuals (28.33 ± 1.32 U/L). In patients with multiple disseminated lesions (78%), the greatest increase in serum ACE activity was observed, followed by those with solitary psoriatic lesions (76%) and erythrodermic psoriasis (31%). Serum ACE activity was significantly decreased in all clinical forms of the disease after the therapy.⁸ Alender et al measured serum and tissue ACE levels in 20 patients with lichen planus before and after therapy, and also in 20 healthy individuals. According to their study, before therapy, serum ACE activity was significantly increased in patients with lichen planus (35.9 ± 2.33 U/L) in comparison to healthy individuals (28.16 ± 1.7 U/L). Tissue ACE activity was increased in patients with lichen planus (2.24 ± 0.41 U/50 mg) in comparison to healthy individuals (1.86 ± 0.16 U/50 mg), but the difference was not significant. After therapy, serum and tissue ACE activity decreased and no significant difference in ACE activity was found.⁹ Robati et al conducted a study of serum ACE levels in pemphigus in which 34 patients with pemphigus vulgaris and 35 healthy individuals were recruited. The mean serum ACE levels in patients and control groups were 25.34 ± 14.25 and 31.97 ± 19.44 respectively. No statistical difference was detected in the mean level of serum ACE of the two groups ($p=0.11$). Furthermore, the mean levels of serum ACE was significantly higher in healthy males compared to male patients ($p=0.045$). Nevertheless, the mean ACE levels was not meaningfully different between the females of two groups ($p=0.90$).¹⁰ Similarly in our study also, the mean serum ACE level was higher in male control than in female controls, but we did not find any significant difference in the patient's group.

Physiologically, sex and age affect the serum ACE level. Benateau-Bernaut et al reported in their study that there was no significant difference in serum ACE levels either by age or by sex in adults, but they noticed higher values in newborns and showed that serum ACE activity returned to the adult value in six-month old infants and stabilized at this concentration by the age of four years. Then, serum ACE gradually increases until puberty; afterward, it decreases during adolescence to reach again to adult values, but ACE activity stays at high values for a longer time in boys than in girls. Such an increment in puberty may be related to a hormonal regulation of ACE synthesis, because it is well known that hormones from the renal cortical and thyroid glands can stimulate ACE biosynthesis, as shown in in-vivo studies as well in in-vitro cultures of endothelial cells.¹¹⁻¹³ On the other hand, the difference encountered between boys and girls during puberty because of testicular and epididymal ACE.¹⁴ In particular, the development during puberty and the maintenance during adulthood of testicular ACE require the presence of an intact pituitary gland, and thus they are

under endocrinological control.¹⁵ ACE2, which is an ACE homolog, is selectively expressed by adult Leydig cells of the testis and it may be one of the reasons of higher serum ACE level in men.¹⁶ Recent study findings are in support of involvement of desmosomes of testis germ cells in pemphigus vulgaris though the pemphigus affects the males and females equally.¹⁷ These studies may support our findings of lower ACE level in male pemphigus patients.

Another similar interesting finding in concurrence with Robati et al study is that the significant increased levels of ACE in patients with cutaneous involvement compared with those with mucosal involvement.¹⁰ It may be due to the skin is a site of ACE expression.¹⁸ However, further studies with larger samples are required to confirm our result.

CONCLUSION

In the current study serum ACE levels are altered in patients with pemphigus vulgaris. Though there is no significant difference in ACE levels in patients and control groups, mean levels was lower in patients. This study also showed a significant difference in the ACE levels between male patients and male controls. This indicates serum ACE can be a useful marker for disease activity in male pemphigus patients.

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