Original paper

Evaluation of total sulfhydryl levels and dietary habits in pemphigus vulgaris

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Abstract

Introduction: Pemphigus vulgaris (PV) is a rare autoimmune bullous dermatitis caused by autoantibodies against desmoglein-1 and desmoglein-3. Sulfhydryl group/total thiols play a key role in numerous cellular activities, such as antioxidant protection, detoxification, cell growth, and apoptosis. Acantholysis may develop due to chemical reasons.

Aim: The aim of this study was to investigate the relationship between PV and serum total sulfhydryl levels.

Material and methods: The study was conducted with a total of 177 individuals, comprising 86 PV patients and 91 controls. Age, gender, smoking status, alcohol consumption, and pemphigus-triggering food intake were recorded. Diagnosis of PV was established based on the clinical and histopathologic examinations followed by a direct immunofluorescence and indirect immunofluorescence test. Serum total sulfhydryl level (TSH) was measured by spectrophotometric method.

Results: Mean age was 41.94 ±11.41 years in the patient group and 39.86 ±11.72 years in the control group. In the PV group, smoking was noted in 62.8% (n = 54) and alcohol consumption was noted in 32.6% (n = 28) of the patients. There was a significant difference in total sulfhydryl levels between the groups.

Conclusions: Our findings suggest that foods and drugs containing sulfhydryl groups may induce pemphigus vulgaris or aggravate the disease.

Key words: diet, pemphigus, sulfhydryl.

Introduction

Pemphigus vulgaris (PV) is a rare autoimmune bullous dermatitis caused by autoantibodies against desmoglein-1 and desmoglein-3. Acantholysis occurs as a result of the disruption of intercellular bridges between keratinocytes and is clinically accompanied by blisters and erosions on the skin and mucosa [1].

Total sulfhydryl group/total thiol (-SH) is an important protein structure and REDOX-reactive group in organisms. Compounds containing sulfhydryl groups are called thiols. Sulfhydryl group/total thiols play a key role in numerous cellular activities, such as antioxidant protection, detoxification, cell growth, and apoptosis. These compounds have been reported to play an essential role in immunopathogenesis of oxidation reactions. Imbalances in the levels of sulfhydryl groups are believed to trigger autoimmune diseases by causing oxidative stress and tissue inflammation [2, 3]. Studies have also suggested that acantholysis may develop due to chemical reasons as well [4]. Pietkiewicz *et al.* suggested that the primary cause of pemphigus in individuals residing near wastewater treatment plants could be related to environmental pollution. The authors also noted that acantholysis may also be caused by chemical substances [5].

Brenner *et al*. suggested that foods containing thiol (sulfhydryl) (onions, garlic, leeks, chives, shallots) are associated with pemphigus [6]. In a previous case report, a 42-year-old female patient developed pemphigus after excessive consumption of leeks and the patient remained in remission for numerous years after the removal of leeks from the diet [7]. In another study, a 49-year-old patient developed pemphigus after exces-

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sive garlic consumption and the disease was brought under control after the removal of garlic from the diet [8]. In a retrospective study conducted by Yavuz *et al.*, the authors suggested that 90% of 130 pemphigus patients consumed sulfhydryl-containing foods [9]. In recent years, many cases of pemphigus caused by drugs containing thiol groups (penicillamine, captopril, bucillamine) have been reported [10].

Although treatments such as prednisolone, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, intravenous immunoglobulins (IVIG) and rituximab are administered in PV patients, the disease sometimes cannot be controlled [11]. This suggests that different treatments are needed for the disease or that these treatments may be aggravating the disease [1].

Aim

The aim of this study was to investigate the relationship between PV and serum total sulfhydryl levels and to contribute to the treatment and control of the disease.

Material and methods

The study was conducted with a total of 177 individuals, comprising 86 PV patients and 91 controls. A written consent form was obtained from all the individuals. The study protocol was approved by the clinical ethics committee and the study was conducted in accordance with the Declaration of Helsinki. Age, gender, smoking status, alcohol consumption, and pemphigus-triggering food intake were recorded. Diagnosis of PV was established based on the clinical and histopathologic examinations followed by a direct immunofluorescence and indirect immunofluorescence test. PV was diagnosed in the presence of flaccid bullae and vesicles on the skin, mucosal erosions, presence of Nikolsky's sign, and typical localizations of the lesions. Additionally, histological examination was performed to analyse the presence and severity of acantholysis and a direct immunofluorescence test was performed to analyse intercellular IgG and C3 deposits (chicken-wire appearance). Finally, serum autoantibodies were evaluated by indirect immunofluorescence assay (IFA). The control group was selected from individuals who applied for cosmetic interventions.

Venous blood samples of 5 ml in total were collected from each patient and control subjects. The blood was allowed to clot for 15 min and then centrifuged at 5000 rpm for 10 min. Separated sera were stored at –80°C until analysis. Serum total sulfhydryl level (TSH) was measured by spectrophotometric method. A total of 100 ml of the sample was mixed with 1,500 ml of potassium phosphate buffer (pH = 7.4, 0.1 M). Immediately after mixing with 400 ml of DTNB solution (2 mM), it was incubated for 5 min at 37°C. The absorbance values of the samples were determined against the reagent blank at 412 nm using Shimadzu UV-1601 spectrophotometer. The extinction coefficient was determined by using emax = 13600 M^{-1} cm^{-1} and the results were given in mmol/l.

Statistical analysis

Data were analysed using SPSS for Windows version 26.0 (IBM Corp., Armonk, NY). Descriptives were expressed as mean, standard deviation (SD), median, frequency (*n*), percentage (%), and minimum-maximum. Normal distribution of continuous variables was assessed using Kolmogorov-Smirnov test, Shapiro-Wilk test, Skewness-Kurtosis, and Histograms. Continuous variables with normal distribution were compared using Independent Samples *t*-test. Categorical variables were compared using Pearson's χ^2 test. A *p*-value of < 0.05 was considered significant.

Results

The study was conducted with a total of 177 cases, comprising 63 (35.6%) men and 114 (64.4%) women with a mean age of 40.87 ±11.59 (range: 20–72) years.

Mean age was 41.94 ±11.41 years in the patient group and 39.86 ±11.72 years in the control group. No significant difference was found between two groups with regard to age ($p > 0.05$). Although there was a female preponderance both in the patient group ($n = 55$ [64%] vs. $n = 31$ [36%]) and the control group ($n = 59$ [64.8%] vs. $n = 32$ [35.2%]), no significant difference was found in both groups with regard to gender distribution ($p > 0.05$) (Table 1).

In the PV group, smoking was noted in 62.8% ($n = 54$) and alcohol consumption was noted in 32.6% ($n = 28$) of the patients. Moreover, excessive consumption of foods containing thiol/sulfhydryl was noted in 41.9% ($n = 36$) and was not noted in 58.1% ($n = 50$) of the patients (Table 2).

Table 1. Demographic characteristics

Parameter		Total ($n = 177$)	Patient group ($n = 86$)	Control group ($n = 91$)	*P*-value
Age [years]	Mean ± SD	40.87 ±11.59	41.94 ±11.41	39.86 ±11.72	[a]0.233
	Median (min.–max.)	40 (20–72)	41.5 (20–67)	38 (20–72)	
Gender, *n* (%)	Male	63 (35.6)	31 (36.0)	32 (35.2)	[b]0.903
	Female	114 (64.4)	55 (64.0)	59 (64.8)	

[a]*Independent samples t test,* [b]*Pearson's* χ^2 *test.*

Table 2. Clinical characteristics of the patient group

Parameter		Patient group (*n* = 86)
Smoking, *n* (%)	No	32 (37.2)
	Yes	54 (62.8)
Alcohol consumption, *n* (%)	No	58 (67.4)
	Yes	28 (32.6)
Excessive consumption of foods containing thiol/sulfhydryl, *n* (%)	No	50 (58.1)

There was a significant difference in total sulfhydryl levels between groups (Table 3).

Table 3. Total sulfhydryl levels in both groups

Group	*N*	Mean ± SD	*P*-value
Patients	86	1.1717 ±0.03375	0.001
Controls	91	0.7340 ±0.02542	

SD – standard deviation.

Discussion

The study showed that serum total sulfhydryl levels are increased in PV patients. To our knowledge, this is the first study investigating sulfhydryl levels in PV patients.

The literature suggests that acantholysis may occur in pemphigus as a result of thiols, tannins, and phenol compounds in the absence of autoantibodies. The effect mechanism of thiols on acantholysis could be explained in several ways: (i) they alter the biochemical structure of the cell, whereby they form cystine-cystine bonds instead of thiol-cystine bonds, (ii) they cause the formation of new antigens by presenting desmosomal proteins to immunological cells, (iii) they affect the plasminogen activating system [6, 12, 13].

An experimental study has shown that certain thiol-allyl compounds (allylmercaptan, allylmethylsulfide, and allylsulfide), found in plants that belong to the genus Allium, i.e. garlic, leek, and onion, can provoke acantholysis in normal human skin cultured *in vitro*. Accordingly, the authors suggested that thiol-containing foods may be associated with pemphigus and thus they should be removed from the diet [14]. Likewise, in a 2001 review by Ruocco *et al*., the authors also suggested that foods containing sulfhydryl groups may induce pemphigus [15]. In our study, a significant portion of the patients consumed thiol-containing foods and the patient group had high levels of thiol, i.e. sulfhydryl, which support the findings of previous studies.

Thiols are available in the structure of many drugs as well as foods. Penicillamine contains a thiol group and is a leading cause of pemphigus. Moreover, it has been reported that approximately 7% of patients using penicillamine develop pemphigus [16]. Captopril, another reported drug related to pemphigus induction, is a commonly prescribed anti-hypertensive agent. It belongs to the angiotensin-converting enzyme inhibitor (ACEi) group, which fall into the thiol group [17]. Bucillamine is another drug containing the thiol group and it has also been reported to induce pemphigus. In a study by Ghaedi *et al*., it was reported that drug-induced pemphigus was caused by drugs containing thiol groups in most of the 170 patients evaluated [18]. Similarly, in our study, thiol groups were found to be a leading cause of PV.

Abida *et al*. examined superoxide dismutase and thiol levels in 13 patients with pemphigus foliaceus and 7 controls and found that thiol levels were lower in lesional and perilesional tissues compared to healthy tissues. Based on these findings, the authors suggested that the autoimmune process is accelerated when the antioxidant system activity is reduced [19]. Although our study was similar to the study by Abida *et al*., it had several remarkable differences because we examined patients with PV and we also evaluated serum sulfhydryl levels of the patients and we had a higher number of participants (*n* = 177). Our findings revealed that the PV patients had higher levels of sulfhydryl, i.e. thiol, compared to controls.

Several studies have evaluated thiol/disulfide levels in dermatologic diseases. Investigations analysing thiol/disulfide levels in conditions such as lichen planus, psoriasis, pityriasis rosea, androgenetic alopecia, and recurrent aphthous stomatitis have shown increased thiol levels relative to disulfide levels. Serum total thiol levels are found to be elevated in acne vulgaris patients. Our findings are consistent with these results [20–25].

Our study was limited in several ways. First, the pemphigus forms other than PV were not evaluated. Second, tissue levels of sulfhydryl (in blister fluid) were not evaluated. Finally, post-treatment sulfhydryl levels were not evaluated.

Conclusions

Our findings suggest that foods and drugs containing sulfhydryl groups may induce PV or aggravate the disease. Multicentre prospective studies are needed to substantiate our findings.

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Ethical approval

Approval number: date and number: 06.08.2019/3.

Conflict of interest

The authors declare no conflict of interest.

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