



A Study on Precipitating Factors in Pemphigus

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Abstract

Background: Pemphigus is the most common cause of morbidity and mortality among dermatological diseases even after treatment with immunosuppressants. There are not many studies on precipitating factors of pemphigus from India.

Aims and Objectives: To identify the precipitating factors in pemphigus.

Methodology: Study was conducted in 30 patients with clinically diagnosed pemphigus in the Department of Dermatology, in a tertiary care hospital in South India. Detailed history of the patients with emphasis on intake of any drugs, moderate or excessive intake of food items with acantholytic potential within one year prior to the onset of the disease were recorded. They were interrogated about history of any unaccustomed physical activity and excessive exposure to sunlight or any surgery in the recent past. Patients were asked whether any injury, burns or infection had occurred recently. Mental stress was assessed using Presumptive Stressful Life Events (PSLE) scale.

Results: Precipitating factors noted were drugs (50%), infections (46.7%), sunlight (43.3%), physical stress (33.3%), mental stress (13.3%) intake of mango (13.3%), tea (10%), onion (10%) and chilly (10%).

Statistical Analysis: All the data were entered in the proforma and were analysed using the statistical package for social science (SPSS) version 10.

Conclusion: Mental stress and infections were found as statistically significant precipitating factors in pemphigus.

Keywords: pemphigus, precipitating factors, acantholytic potential.

Introduction

Pemphigus refers to a group of acquired, life threatening autoimmune blistering disorders presenting clinically as flaccid intraepidermal blisters, erosions and ulceration on skin and mucosa. It is associated with IgG antibodies targeting keratinocyte antigens like desmogleins and eliciting epidermal clefting (acantholysis) via intracellular signaling activating apoptotic enzymes (apoptolysis).¹ It is an uncommon disease, varying in incidence from 0.09 to 1.8%.²

The onset and course of pemphigus is often the result of an interaction between predisposing genetic factors and environmental precipitating factors. Genetic susceptibility to pemphigus has been linked to HLA alleles DRB1 and DQB1. Triggering factors so far reported include physical agents (heat, sunlight, surgery), drugs, pesticides, infections, emotional stress and dietary factors. Disease may occur when genetically susceptible persons are exposed to these inducing agents.³

The acronym PEMPHIGUS was proposed to summarize these factors: Pesticides, Malignancy, Pharmaceuticals, Hormones, Infectious agents, Gastronomy, Ultraviolet radiation and Stress.⁴ Avoiding or limiting the precipitating factors may be a useful precaution in the management since it can reduce relapses and improve efficacy of treatment. There are not many studies on precipitating factors of pemphigus from India.

Materials & Methods

Descriptive study was done in the Department of Dermatology and Venereology in a tertiary care hospital, South India. All new clinically diagnosed cases of pemphigus attending the department were included in the study. 30 patients were studied during this period.

After getting consent, history of the patients were taken including age of onset of the disease, duration and site of onset of the lesions. Detailed history of the patients with emphasis on intake of any drugs and moderate or excessive intake of food items with acantholytic potential like garlic, tea, mango etc. within one year prior to the onset of the disease were recorded. They were interrogated about history of any moderate increase in or any unaccustomed physical activity and moderate or excessive exposure to sunlight. Patients were asked whether any injury (minor or major), burns (mild or severe) or infection had

occurred in the recent past. Any history of surgery (minor or major) in the recent past was also asked. Mental stress was assessed by a Psychiatrist. It was also assessed using Presumptive Stressful Life Events (PSLE) scale developed by Gurmeet Singh et al⁵. During dermatological examination, sites of involvement on both skin and oral lesions were recorded. Diagnosis was confirmed by cytology, histopathology or by direct immunofluorescence studies. All data were entered in the proforma and were analysed using SPSS version 10 software. The associations and comparisons between different parameters were elucidated using the nonparametric test i.e. chi square (X²) test. A two-tailed distribution was assumed for all statistical evaluations and probability value <0.05 was considered significant.

Results

In the study group of 30 patients, male to female ratio was 1:1. Majority (63.3%) of the patients were in the age group 30 –59 years of which 33.3% in 45-59 year group. Among male patients, positive history of smoking was present in 46.7%. Upper trunk (89.3%) was the commonly involved site followed by limbs (82.1%), scalp (57.1%), lower trunk (53.6%), and face (46.4%). 27 cases (90%) had mucosal involvement. Distribution of mucosal lesions shown in Figure 1.

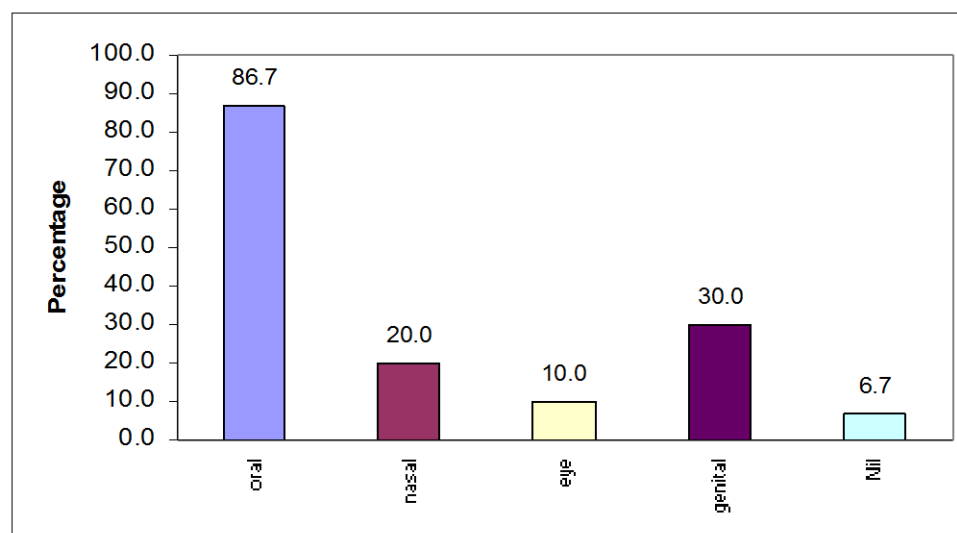


Figure -1 Distribution of mucosal lesions

History of intake of antibiotics prior to the onset was given by 26.7% and 40% had taken nonsteroidal anti-inflammatory drugs (NSAIDs) including paracetamol. Of the 15 patients (50%) with history of drug intake, 53.4% had interval between 1 day to 1 month. 33.3% had interval of >121 days. No history of exposure to pesticides was obtained in any patients.

Nineteen (63.3 %) patients gave history of intake of moderate or excessive amounts of food items with known acantholytic potential. 13.3% had history of intake of mangoes, 10% each with intake of tea, onion and chilly and 6.7% each for garlic and grapes. History of moderate or unaccustomed physical stress preceding the onset was obtained in 18 (60%) patients. History of exposure to sunlight (43.3%), physical activity (33.3%), surgery (13.3%), burns (10%), and heat (6.6%) was present. Mental stress or pathology was observed by Psychiatrist in 5 (16.7%) cases. According to the PSLE score, 23 (76.6 %) patients experienced moderate or severe mental stress prior to the onset of the disease (Table –1).

Table 1 Mental stress

PSLE score	Count	Percent
Mild	7	23.3
Moderate	19	63.3
Severe	4	13.3
Average	104.5 ± 87.5	

$$\chi^2 = 12.6, p=0.002$$

Out of nine cases of viral infections which preceded the disease, five were Chikungunya fever and four were other viral fevers. Of the five patients (16.7%) who had bacterial infections, one had respiratory tract infection and two each had abscesses and dental caries. Table 2 shows details of viral and bacterial infections.

Table 2 -Infection

Infection	Count	Percent
No	16	53.3
Viral	9	30.0
Bacterial	5	16.7

$$\chi^2 = 6.2, p=0.045$$

Discussion

Out of the 30 patients with clinically diagnosed pemphigus studied, male to female ratio was found equal (1: 1) in our study. But there was a female predominance 61.5% in the study by Ajithkumar K.⁶

Majority of our patients were in the age group 30 –59 years (63.3%) with an average age of 46.1 years. This was almost similar to the study by Chams-Davatchi et al⁷ (42 years).

Seven (23.3%) patients had history of smoking. Among male patients, 53.3 % were non –smokers. But few of the patients with pemphigus (17.1%) reported a current or past history of smoking, which was statistically different from the control group (27.3% smokers) in a study by Valikhani M et al. The duration of smoking and the number of cigarettes smoked daily was also significantly lower in this patients.⁸ This is due to the presence of cholinergic agonist, nicotine in cigarette smoke which may interfere with the activity of the antibody to keratinocyte acetylcholine receptor.⁹ Whether smoking has got a protective role needs further case - control studies.

Upper trunk (89.3%) was the commonly involved site followed by limbs (82.1%), scalp (57.1%), lower trunk (53.6%), and face (46.4%). This was not in conformity with the analysis done by Chams-Davatchi et al⁷. The majority of lesions were observed on the thorax in 70%, scalp 49%, face in 44% , flexor aspect of limbs in 40%, extensor aspect in 37 % , abdomen in 40%, and generalized lesions in 20%.

Among the twenty seven (90%) cases who had mucosal involvement, oral mucosa was involved in majority (86.7%) followed by genitalia (30%), nasal (20%), and eyes in (10%). And in the study by Svecova D et al,¹⁰ mucosal lesions in the oral cavity were found in 77.3% patients not conforming to our study. Other mucous membranes affected were in nasal mucosa in 9.1%, genital mucosa in 20.5%, laryngeal mucosa in 13.6%, rectal mucosa in 9.1%, conjunctiva in 9.1%, and esophageal involvement in 4.5% patients.

Precipitating factors

Precipitating factors noted were drugs (50%), infections (46.7%), sunlight (43.3%), physical stress (33.3%), mental stress (13.3%) intake of mango (13.3%), tea (10%), onion (10%) and chilly (10%). But during analysis of 155 patients by Mimouni D, only in 10% a potential precipitating factor could be identified.¹¹

In the present study, history of intake of antibiotics was present in 26.7%, 23.3% patients consumed nonsteroidal anti-inflammatory drugs and 16.7% gave history of intake of paracetamol. In the 11 year review of 31 patients by Chmurova N and Svecova P¹² history of drug intake prior to the onset of the disease was present, but at a lower rate of 12.9%. In the study by Akarsu et al¹³, drugs that might have been triggers were found to be only metoprolol and paracetamol (3.8%) each. The various drugs found to induce pemphigus were diclofenac, ACE inhibitors, acetylsalicylic acid, propionic acid derivatives, levodopa and INH in the 11 year study¹², and penicillin in the case – cohort study of 363 patients from Israel by Heymann AD.¹⁴

Certain drugs provoke acantholysis by interfering with the keratinocyte membrane biochemistry (biochemical acantholysis) and/or with the immune balance (immunologic acantholysis).³ 53.4% had interval between 1 day to 1 month. 33.3% had interval of >121 days. The interval between drug intake and the disease onset was in conformity with the study done by Brenner S et al¹⁵.

13.3% had history of intake of mangoes, 10% each with intake of tea, onion and chilly and 6.7% each for garlic, eggs, banana and grapes. Partially correlating with the present study, triggering foods implicated were tomato in 23.1%, garlic in 15.3%, onion, orange, and black pepper in 11.5%, leek, banana, and red pepper in 7.7%, and strawberry, grape, iodized salt, and sea fish in 3.8% of the 26 pemphigus patients by Akarsu et al¹³. Dietary molecules with acantholytic potential include thiols (garlic, onion), thocyanates (mustard oil), phenols (fruits) and

tannins (mango, tea, chilly). The molecular structure of many food ingredients are found similar to the known pemphigus antigens.¹⁶

In the study group, 43.3% of pemphigus vulgaris patients had history of moderate to severe sun exposure prior to the onset of the disease. Various studies have found sunlight as a precipitating factor in pemphigus, but at a lower rate. It was 3.7% (Chmurova N et al)¹² and 18% in a study done at Israel by Wohl Y and Brenner S.¹⁷ Increased number of Dsg1 and Dsg3 epitopes may be uncovered during UVB exposure and become available to react with the pathogenic antibodies.

History of surgery (13.3%) and injury (3.3%) were present preceding the onset of disease in the present study. Akarsu et al¹³ identified physical trauma as a precipitating factor to a higher extent in pemphigus cases 42.3%. Also in the study done by Chmurova N et al, 6.5% cases had history of mechanical irritation preceding the disease.¹² 10% had history of burns, 6.6% had history of exposure to heat in our study. There are reports of pemphigus vulgaris following burns and radiotherapy (Robbins AC et al).¹⁸ Radiation may release previously sequestered antigens, modify antigenic targets or decrease immunosurveillance. Mental stress Severe stress was found in 13.3% patients. This is in conformity to the review done in 31 cases by Chuamovra (16.1%).¹² The analysis done by Sustic et al¹⁹ found stressful events have the potential in development of pemphigus but with a higher rate.

In the study group, 30% patients had viral infections which is in conformity with the 11 year review (38.7%).¹² In our study, 55.6% of the viral infections were Chikungunya fever. Viruses which were found to be associated with pemphigus include varicella zoster, Epstein – Barr, cytomegalovirus, human herpes virus 6 and HHV-8 (Wang GQ et al).²⁰

16.7% cases had history of bacterial infections in our study. Bacterial infections were observed in 35.5% cases preceding the onset and dental caries in 25.8% (Chmurova N et al).¹² at a higher rate and bacteria such as coagulase- positive

Staphylococcus aureus.⁴ The precipitating effect might be due to interferons and other cytokines released by the host as a consequence of the viral attack, which over activate the immune response.³

Conclusion

Mental stress and infection were found as a statistically significant factors in the occurrence of the disease. Other common precipitating factors noted were drugs and sunexposure. Evaluation of triggering factors before starting treatment may assist in controlling the disease more rapidly and reducing the dose and therefore the side effects of immunosuppressants during treatment of pemphigus. Patient can be advised to have special caution while sunexposure, intense emotional stress, certain drug intake and eating foods that have an acantholytic potential. But follow - up studies with a control group is necessary for confirming them as precipitating factors in the disease.

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