

Pemphigus Disease: A geoepidemiologic preliminary study in Iran

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Objectives Pemphigus is an autoimmune, life-threatening, blistering disease. Knowledge about the epidemiology of this disease however, is still limited. The aim of this study was to investigate the frequency and geographic distribution of pemphigus patients in Iran.

Methods Medical records of patients with definitive diagnosis of pemphigus disease during a seven-year period from March 2006 to March 2013 were retrospectively reviewed. All individuals were classified based on geographical aspects.

Results A total of 110 patients (59 females and 51 males) with an average age of 46.5 ± 13.6 for the females and 45.8 ± 12.5 for the males were evaluated. Male patients were slightly younger than female patients, but the difference was not statistically significant. Also, there was no significant association between age and the year of frequency. The most frequent type of pemphigus was the vulgaris type (93.6%). On the base of climate, the highest frequency was seen in the Moderate to severe internal (very hot) desert area and the humid and temperate climates (Caspian). There was no significant difference between the mean ages of pemphigus patients in the four geographic regions, (P value=0.421). Based on altitude in each climatic region, less than 10% of patients were from high altitude areas.

Conclusion Environmental factors are important in frequency of autoimmune disease including pemphigus. We concluded that the frequency of pemphigus disease might be different in different climates and altitude. Further research towards the improvement of data on the geographical study could open up a field to identify the patterns of pemphigus disease.

Keywords Autoimmune disease; Pemphigus; Climate; Geography

Introduction

Autoimmune diseases include many heterogeneous disorders of largely unknown etiology that is thought to occur as a result of interactions between genetic and environmental factors, leading to immune responses against self-antigens.¹ Pemphigus is a group of autoimmune, potentially life-threatening, intra-epidermal blistering diseases that result in erosions and large areas of denuded skin and mucous membranes. It most frequently occurs in the fifth and sixth decades of life.^{2, 3} Pemphigus vulgaris and pemphigus foliaceus are two major variants. Any mucosal and skin surface may be affected. Oral involvement is frequent in up to 80% to 90% of patients with pemphigus vulgaris. Most importantly, oral lesions are the first symptom in about two-thirds of the cases. Coexistence with other autoimmune diseases has been reported in some cases of pemphigus vulgaris.^{2, 3} The epidemiology of pemphigus diseases is not yet clear.

Many studies have reported that chronic high-altitude exposure can induce complicated structural and pathophysiologic changes in many systems and organs. There are some geoepidemiologic studies on autoimmune diseases that found that climatic and altitudinal factors might be partly responsible for development of human autoimmune disorders. One of the most striking examples is

the strong gradient in the prevalence of systemic sclerosis in relation to distance from the equator. Another study indicated that altitude might be closely related to the pathogenesis and development of systemic lupus erythematosus (SLE).^{1, 4, 5} Also, a review of epidemiological data has shown that pemphigus frequency varies according to the region.² Based on examination of epidemiological studies in various populations, researchers suggested that the frequency of this disease might be influenced by the latitude.⁶ The aim of this study was to investigate the frequency and geographical distribution of pemphigus in Iran.

Materials and Methods

Study site: The country of Iran, which is located in the southwest Asia, at the latitude of 250 to 400 of North, and geographical longitude of 440 to 640 of East, is a large area of Iranian flat. Iran has different altitudes and a widely varying climate. A previous study indicated that the altitude of Iranian cities varied from 26 to 2790 meters above the sea level.⁷ The climate of Iran can be classified into six major climatic regions based on three factors of humidity, temperature, and wind direction using the Köppen climate classification. Therefore, the country serves as an excellent sampling zone for geoepidemiologic evaluations.⁸

Ethics and Sample: Prior to commencing the study, ethical approval was obtained from Shahid Beheshti University of Medical Sciences. The database of a dermatology clinic, which is a leading referral center for pemphigus disease in the capital city of Iran was evaluated. All patients presenting to the dermatology department of this clinic during a seven-year period from March 2006 to March 2013 with a diagnosis of pemphigus were included. The diagnosis of pemphigus was confirmed based on histopathological and immunofluorescence studies for each patient, carried out by dermatologists. The gender of patient, age at diagnosis, the subtype of pemphigus, year of diagnosis and geographical region (from birth to diagnosis of the disease) were recorded. The location was the patients' primary city of residence according to their declaration (and we assumed that patients remained in this location – a not unreasonable assumption in the current socio-economic status of Iran).

A total of 115 patients were investigated (5 of them were excluded because of incomplete data). We classified all individuals into 6 climatic regions: Humid and temperate climatic region (Caspian Sea) (A), the semi-arid climate (B), climatic region of Zagros (C), very hot coastal desert climate (D), moderately or severely hot internal desert areas (E), and warm to hot desert climate (F) based on a previous study.⁸ (Figure 1) The altitude of each province in the defined climatic regions was also categorized into three strata based on the average altitude above the sea level: low (<1500 m), moderate (1500-2000 m) and high (>2000 m) according to Qian et al. (2014)⁴ (Figure 1)

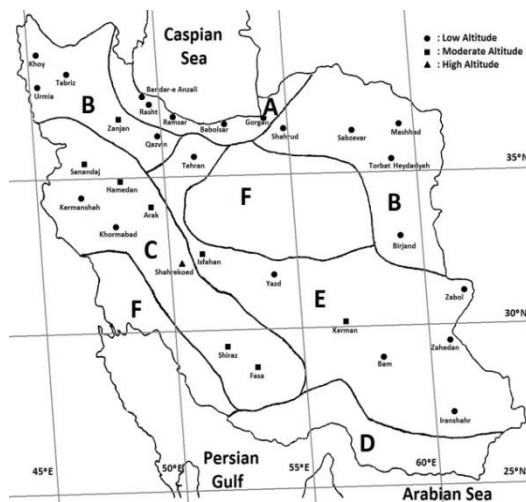


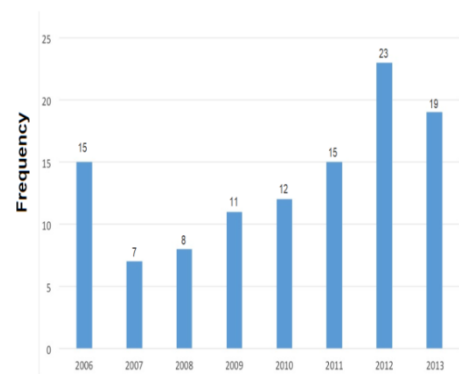
Figure 1- Climatic and altitude classification of Iran

Analysis: Data management and analysis were performed using SPSS version 18.0 (SPSS Inc., IL, USA). Distribution of pemphigus patients was assessed by descriptive statistics. We used independent-sample t-test and one-way ANOVA to find differences. Statistical significance was set at $p < 0.05$.

Results

The study included a total of 110 patients (59 females and 51 males). The mean age of patients was 46.5 ± 13.6 years for females and 45.8 ± 12.5 years for males; this difference was not statistically significant ($P=0.7$). Most patients had more than one involvement sites, and the exact involvement site had not been recorded. However, generally, the most common intraoral site of involvement was the buccal mucosa (60 patients). Floor of the mouth had the lowest frequency. Among the extra-oral sites of involvement, pharynx and skin had the highest frequency and conjunctiva had the lowest, respectively.

The annual frequency of pemphigus disease is shown in Graph 1. There was no significant difference in the mean age of patients in different years.



Graph 1- Frequency of pemphigus patients in each year

($P=0.15$; Table 1). The most frequent type of pemphigus disease was the vulgaris type (93.6%), followed by foliace (5.4%) and vegetans (1%), respectively. Patients were only found to be residents of A, B, C, and E climatic regions. The majority of patients were from the moderately to severely hot desert areas and the humid and temperate climates (Caspian Sea; Table 2). The exact population in each climatic region was not available; however, best estimate of the population showed that after rate adjustment, regions E and A still had the highest frequency of disease cases. Based on the altitude of each climatic region, we found that less than 10% of patients were from high-altitude regions (Table 2). There was no significant difference between the age of pemphigus patients in the four geographic regions, ($P=0.421$; Table 3).

Table 1- Average age of patients in each year

Year	Average age	Maximum Age	Minimum Age	Standard deviation
2006	39.9	59	22	13.1
2007	42.3	53	32	7.2
2008	40.4	62	24	13.1
2009	48.5	75	32	11.4
2010	49.4	65	23	16.2
2011	46.5	68	24	12.6
2012	51.6	80	33	12.6
2013	45.4	71	20	12.6

The most frequent type of pemphigus was the vulgaris type (93.6%), followed by foliace (5.4%) and vegetance (1%)

respectively. Patients were only found to be resident in A, B, C, and E climatic regions. Most commonly patients were from the Moderate to severe very hot desert area and the humid and temperate climates (Caspian) (Table 2).

Table 2- Frequency of pemphigus in each climatic region

Regions	Altitude	Population/10 ⁶	Frequency	Percent
A	Low	7.3	23	20.9
B	Low to moderate	20.8	5	4.5
C	Moderate to high	16.2	11	10.0
E	Low to moderate	23.5	71	64.5
Total		67.8	110	100

Table 3- Average of age in each climatic region

Regions	Average age	Maximum Age	Minimum Age	Standard deviation
A	46.3	75	24	14.5
B	47.6	57	34	8.7
C	40.0	58	20	14.6
E	47	80	22	12.5

Discussion

According to the results, the mean age of females and males was 46.5 and 45.8, respectively. Similar observations have been reported in Tehran⁹, northeast Iran¹⁰, center of Iran¹¹ and west of Iran.¹² However, the highest frequency of cases worldwide have been reported in the fifth and sixth decades of life.⁹ It seems that the onset of disease is earlier in Iran and the reason is unknown.

Pemphigus vulgaris was the most commonly observed clinical variant in this study, (93.6%). This finding was in line with the results of another long-term study in Iran (9).

Female predominance was observed in the present study (male to female ratio: 1:1.15). Although higher frequency of disease in females has been reported in most studies, this proportion varied in different investigations.^{12, 13} For instance, Esmaili et al. (2008) found the ratio of 2.1:1 in their study in Iran; while another study in the west of Iran reported 1.04:1 ratio of females to males.^{12, 14}

Trend of pemphigus over time was erratic in the present study, with the highest frequency in 2012 and the lowest frequency in 2007. Although we could not find any previous study comparing the time trend of pemphigus in Iran, a study performed on 1,209 pemphigus patients in Tehran, reported an annual frequency of 1.6 out of 100,000.¹³ This is much more than 0.24 in 100,000 people that was reported in the Iran's neighboring country, Turkey.¹⁵ In our study, more than two thirds of patients came from moderately to severely hot desert areas, and humid temperate climates, followed by Zagros and semi-arid climatic region.

Wide variations in the prevalence of autoimmune disease are reported in different geographical regions. In a systematic review on epidemiology of multiple sclerosis in Iran, authors reported diversity in distribution of multiple sclerosis

according to geographical classification.¹⁶ Meyer and Misery⁶ reviewed the geoepidemiologic factors related to the prevalence of pemphigus in different countries and strongly recommended that the frequency of disease is higher in lower latitudes and lower in higher latitudes. They reported that most available studies on this topic have evaluated the Mediterranean Basin or the Middle East and little is known about the epidemiology of pemphigus in the Western Europe, which may be indicative of higher frequency of pemphigus in the former regions.

Although we could not significantly associate the prevalence of pemphigus with latitude in this study, the high rate of pemphigus in region A (with high latitude), and lack of any cases in region D (with low latitude) indicated results opposing to that of Meyer and Misery.⁶ However, a multicenter study across different latitudes is recommended to better elucidate this topic. Finally, in addition to latitude and climate, altitude might be associated with structural and pathophysiologic changes in immune function because of chronic hypoxia in high altitudes. Almost all important body organs and systems are affected by long-term high-altitude exposure.^{1, 4} Our hypothesis was based on previous studies^{4, 17} on the role of altitude on autoimmune disease, which indicated that altitude might be related to the pathogenesis and development of pemphigus.

It is important to note that there has been no standard definition for "high" altitude. Considering the minor physiological effects observed at altitudes below 2000 m, we categorized cities above 2000 m from the sea level as high altitude.^{4, 17} In terms of altitude, we found that less than 10% of patients were from high-altitude areas and more than 25% were from low-altitude regions. There were no significant differences between the ages of pemphigus patients in four geographic regions found in the present study.

Qian et al. (2014)⁴ explored the correlation between the activity of SLE and altitudinal variations on 1029 patients in China. They could not find any significant correlation between SLE activity and altitude. However, they found that the age of onset of SLE in patients at high altitudes was significantly younger than that at low and moderate altitudes, and the age of SLE patients at the time of admission at low altitudes was significantly older than that at moderate and high altitudes. Generally, they recommend that altitude affects some clinical features, laboratory tests and activity of main organs in SLE.

Conclusion

Little geoepidemiological data are available for pemphigus disease. Although we explored 7-year data from a leading pemphigus center in Iran, it is just a preliminary study in terms of the association of geographical factors with pemphigus disease, and had some limitations. Considering the significant effect of environmental factors on the frequency of autoimmune diseases, expanded multilateral geographical

studies for pemphigus disease is strongly recommended.

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Conflict of Interests

None Declared ■

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