Acta Dermatovenerol Croat 2017;25(3):181-188 ORIGINAL SCIENTIFIC ARTICLE

Epidemiology of Pemphigus in Turkey: One-year Prospective Study of 220 Cases

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ABSTRACT Pemphigus is a group of rare and life-threatening autoimmune blistering diseases of the skin and mucous membranes. Although they occur worldwide, their incidence shows wide geographical variation, and prospective data on the epidemiology of pemphigus are very limited. Objective of this work is to evaluate the incidence and epidemiological and clinical features of patients with pemphigus in Turkey. All patients newly diagnosed with pemphigus between June 2013 and June 2014 were prospectively enrolled in 33 dermatology departments in 20 different provinces from all seven regions of Turkey. Disease parameters including demography and clinical findings were recorded. A total of 220 patients were diagnosed with pemphigus during the 1-year period, with an annual incidence of 4.7 per million people in Turkey. Patients were predominantly women, with a male to female ratio of 1:1.41. The mean age at onset was 48.9 years. Pemphigus vulgaris (PV) was the commonest clinical subtype (n=192; 87.3%), followed by pemphigus foliaceus (n=21; 9.6%). The most common clinical subtype of PV was the mucocutaneous type (n=83; 43.2%). The mean Pemphigus Disease Area Index was 28.14±22.21 (mean ± Standard Deviation). The incidence rate of pemphigus in Turkey is similar to the countries of South-East Europe, higher than those reported for the Central and Northern European countries and lower than the countries around the Mediterranean Sea and Iran. Pemphigus is more frequent in middle-aged people and is more common in women. The most frequent subtype was PV, with a 9-fold higher incidence than pemphigus foliaceus.

KEY WORDS: pemphigus, epidemiology

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INTRODUCTION

Pemphigus is a group of rare and life-threatening autoimmune bullous diseases of the skin and mucous membranes which result in intraepidermal blistering. It is associated with pathogenic antibodies directed against desmoglein (Dsg) 3 and/or Dsg 1, two transmembrane components of desmosomes, and cell-cell adhesion complexes (1).

Pemphigus is a rare disease with an incidence range from 0.5 to 32.0 per 1 000 000 in different geographic areas and ethnic groups (2). Pemphigus vulgaris (PV) and pemphigus foliaceous (PF) are the main clinical subtypes of the disease. PV often affects individuals during the fourth and fifth decades of life, and its main characteristics are flaccid blisters and erosions of the mucous membranes and the skin. The most characteristic clinical findings are painful erosions and ulcers in the oral mucosa. In contrast, scaly crusted erosions with an erythematous base are often observed in PF on the seborrheic regions such as the face, scalp, chest, and back without mucosal involvement (1).

Few prospective data are available about the epidemiology of pemphigus. In the Turkish population, there is so far only one prospective study, which found the yearly incidence of pemphigus to be 2.4 per 1 000 000 in the Mediterranean region of Turkey (3). The aim of this multicenter one-year prospective study was to evaluate the incidence, epidemiological, clinical, and immunologic features of patients with pemphigus in broader Turkey.

PATIENTS AND METHODS

Patients, demographic and clinical presentation

Patients with a suspected diagnosis of pemphigus who had been referred to one of the 33 dermatology departments of university or training and research hospitals in 20 different provinces from all geographic regions of Turkey (Figure 1) were prospectively enrolled in the study if they had a newly confirmed diagnosis of pemphigus and gave informed written consent. Data were collected for the patients with pemphigus diagnosed for the first time between 1 June 2013 and 31 May 2014. The study was approved by the ethics committee of Akdeniz University.

The following demographic and clinical data were recorded for all patients: sex, age, age at onset, geographic history, symptoms at onset, symptoms at the time of diagnosis, chronology of the symptoms, clinical findings, subtype of disease, severity, and laboratory findings.

The severity of disease was evaluated using the Pemphigus Disease Area Index (PDAI) which was developed by the International Pemphigus Committee. PDAI has a potential range of 0 to 263 (120 points for skin activity, 120 points for mucosal activity, 10 points for scalp activity, and 13 points for postinflammatory hyperpigmentation (PIH)). The scores are defined for different anatomic regions based on the number and size of the lesions (4).

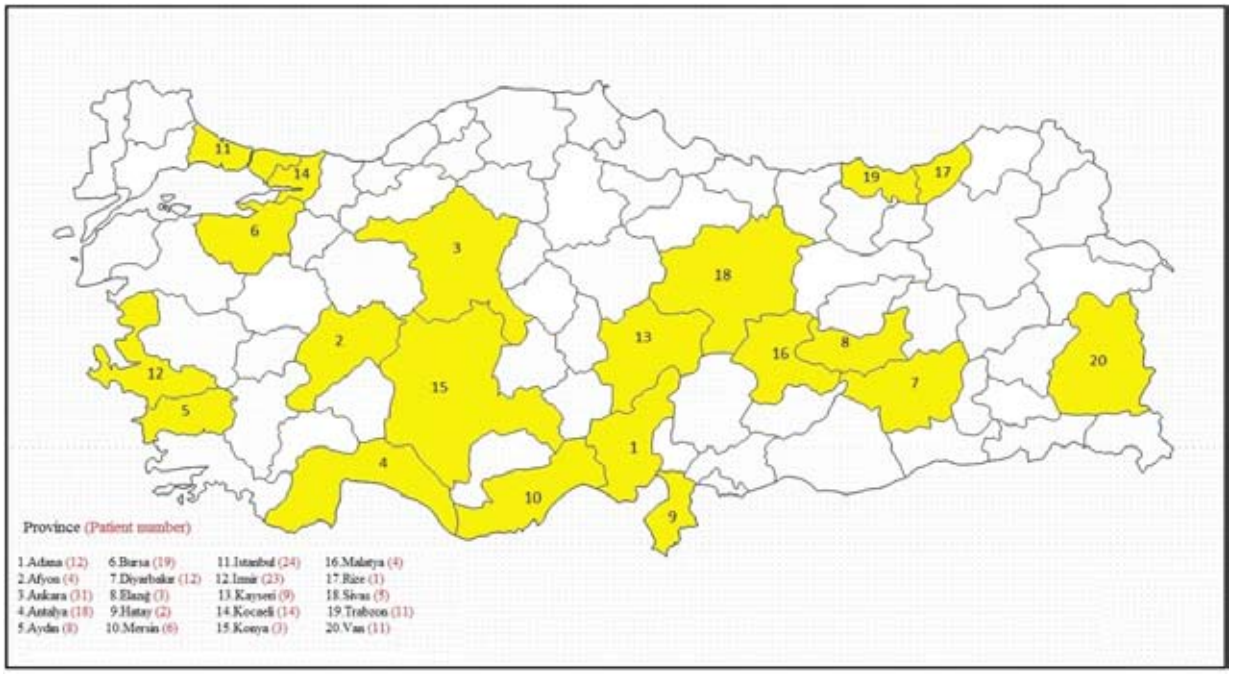

Figure 1. The provinces of Turkey (numbered and marked with yellow) where the centers our study was conducted in are located and the number of recruited patients.

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Diagnosis of Pemphigus

At least three samples were taken from each patient to confirm the diagnosis of pemphigus. Two of them were skin biopsies for histologic examination from lesional skin and for a direct immunofluorescence test (DIF) from perilesional skin. Paraffin and frozen sections were performed on the skin samples for histological examination and DIF, respectively. A classical DIF technique was carried out using fluorescein-isothiocyanate conjugated polyclonal sheep antihuman-IgG, -IgA, -IgM, -C3, and fibrinogen antibodies. The third sample was serum from blood samples for immune serologic examination using the commercially available anti-Dsg1 and anti-Dsg3 ELISA kit and/or indirect immunofluorescence test (IIF). The diagnosis of pemphigus (Figure 2) was based on five criteria: (i) typical clinical presentation with mucosal and cutaneous blisters and erosions for PV or scaly crusted erosions and flaccid blisters without mucosal involvement for PF; (ii) histopathological evidence of intraepidermal blistering with acantholysis; (iii) IgG deposits on the surface of epidermal keratinocytes (PV, PF) and at the dermal-epidermal junction (PNP/PAMS, PE) of perilesional skin by DIF microscopy; (iv) presence of circulating IgG autoantibodies binding to the cytoplasmic membrane of stratified epithelia (normal human skin or monkey esophagus epithelium); and/or (v) serological detection of anti-Dsg3 and/or anti-Dsg1 IgG autoantibodies by a commercially available ELISA test (Euroimmun, Luebeck, Germany). The presence of (i) and (ii) in addition to either (iii), (iv), or (v) were mandatory for the establishment of a diagnosis of a new case of pemphigus.

Statistical analysis

Using data for the Turkish population provided by Turkish Statistical Institute (http://www.turkstat.gov.tr), we calculated the mean incidence with their 95% confidence interval (CI). Twenty provinces are listed below in alphabetical order: Adana, Afyon, Ankara, Antalya, Aydın, Bursa, Diyarbakır, Elazığ, Hatay, Istanbul, Izmir, Kayseri, Kocaeli, Konya, Malatya, Mersin, Rize, Trabzon, Sivas, Van. In the study period, 2013-2014, the mean Turkish population consisted of 77 181 884 persons, of whom 46 382 628 were inhabitants of those 20 provinces. The incidence was defined and computed as the number of patients with a newly confirmed diagnosis of pemphigus in this particular year divided by the total number of inhabitants of those 20 provinces.

Statistical analysis was performed on SPSS 16.0 software. Constant variables in the data set were expressed as mean, median, Standard Deviation, and minimum and maximum values, while categorical variables were expressed as frequency and percentage.

RESULTS

Patients, demographic, and epidemiological data

In total, 252 patients were initially included in this multicenter one-year prospective study. Thirty-two patients who were diagnosed with pemphigus without DIF or ELISA were excluded from the final analysis. A total of 220 patients, including 129 (58.6%) women and 91 (41.4%) men, with a female/male ratio

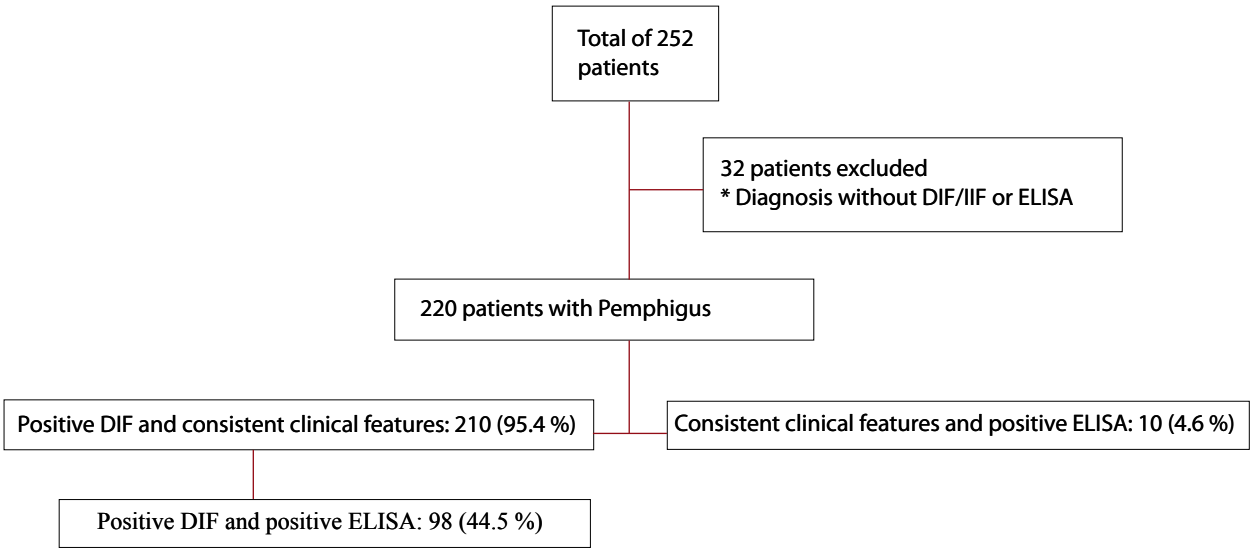

Figure 2. Flow chart of study methods with diagnostic criteria for pemphigus

of 1:1.41, were studied (Table 1). The mean incidence of pemphigus was 4.7 new cases per million people per year (95% confidence interval (CI) 4.1-5.4).

The age range of the onset of the disease was 20-96 years (mean ± Standard Deviation: 48.92±15.02). All patients were older than 20 years of age. The mean time period between the onset of the disease and the definite diagnosis was 6.45±8.32 months. The shortest time to diagnosis was 5.87±7.17 months for PV, and the longest was 12.35±15.06 for PF.

Sex ratio and age distribution

There was a female predominance with a male to female ratio of 1:1.41. The mean age of onset was 48.92±15.02. Patients with PV had a younger age of onset than patients with PF (48.13±14.36 vs. 51.85±19.77). Men were approximately 1 year younger than women (48.86±14.17 vs. 49.97±15.99).

Clinical subtypes

Pemphigus vulgaris was the most common clinical subtype, identified in 192 patients (87.3%), with an approximately 9-fold higher incidence than PF. Pemphigus foliaceus was diagnosed in 21 patients (9.6%). The other subtypes were rarely diagnosed, as shown in Table 1.

Clinical presentations

Oropharyngeal mucosa was the most common site of onset (54.1%) in pemphigus. In 118 (61.4%) patients with PV, persistent oral ulcers and erosions were the onset manifestations; the skin involvement occurred with an average lag period of 3.06±4.62 months. In 9 (4.6%) patients with PV, oropharyngeal mucosa and skin were both involved simultaneously at the onset. In 63 patients (32.8%) with PV and all patients with PF, pemphigus erythematosus (PE), pemphigus herpetiformis (PH), pemphigus vegetans (PVg), and drug-induced pemphigus, the onset was at the skin and limited only to the skin. Larynx involvement with hoarseness was detected in 35 (15.9%) patients, 34 of them were diagnosed with PV. The conjunctival mucosa was involved in 17 (7.7%) patients; all of these patients were also diagnosed with PV. Regarding nasal involvement, 18 (8.1%) patients, all PV, had nasal erosions. In 149 patients (67.7%), the number of lesions were more than 10. The mean PDAI score of all patients was 28.14±22.21, consistent with moderate to severe disease.

Diagnosis

According to diagnostic features, the largest group with 210 patients (95.4%) were the patients with typical clinical characteristics of pemphigus and positive direct IF. Ninety-eight patients (44.5%) in this group also had positive tests for ELISA. Additionally, in 10 patients (4.6%) the diagnosis was established with consistent clinical features and positive ELISA.

Table 1. Demographics and clinical features of 220 patients with pemphigus

Sex (men:women)	1:1.41
Mean age ± SD (year)	49.51±15.24
Age range (years)	20-96
Mean age of onset ± SD (year)	48.92±15.02
Subtype of pemphigus (n, %)	
Pemphigus vulgaris	192 (87.28)
Pemphigus foliaceus	21 (9.55)
Pemphigus vegetans	1 (0.45)
Pemphigus erythematosus	3 (1.37)
Paraneoplastic pemphigus	1 (0.45)
Pemphigus herpetiformis	1 (0.45)
Drug-induced pemphigus	1 (0.45)
Clinical type of pemphigus vulgaris (n, %)	
Mucocutaneous	83 (43.2)
Mucosal	69 (35.9)
Cutaneous	40 (20.9)
Location at onset (n, %)	
Oropharyngeal	119 (54.1)
Cutaneous	90 (40.9)
Both	11 (5.0)
The number of lesions (n, %)	
<3	8 (3.6)
3-5	10 (4.6)
6-10	53 (24.1)
>10	149 (67.7)
Severity of disease (mean PDAI ± SD)	28.14±22.21
The mean time to diagnosis ± SD (month)	6.45±8.32

*SD: Standard Deviation; PDAI: Pemphigus Disease Area Index

Regarding ELISA tests, less than half of the patients had these test results due to clinical limitations. More than 90% sera showed anti-Dsg reactivity in the PV group; 97% (96 of 98 patients) for anti-Dsg3 and 91% (89 of 98 patients) for anti-Dsg1.

Associated diseases, concomitant medications, and family history

The most significant associated disease was concurrent hypertension in 15 patients (6.8%). Other associated diseases were diabetes mellitus in 5 patients and goiter, asthma, and hyperlipidemia in 3 patients. At the time of diagnosis, 13 patients (5.9%) were being treated with cardiovascular drugs (7 patients with angiotensin-converting enzyme inhibitors, 4 patients with angiotensin receptor blockers, and 2 patients with beta blockers). Two patients were on cephalosporins, and one patient was on d-penicillamine. Fourteen patients were recorded as using different

Table 2. Demographic characteristics and incidence of pemphigus in different countries

Authors	Study design	Country	Patient (n)	Sex (F: M)	Mean age (years)	Incidence (cases/million)
Cordel *et al.* (29)	Prospective	Guadeloupe	15	1.14	53	6.96
Huang *et al.* (28)[a]	Prospective	Taiwan	853	1.3	52.5	4.70
Zaraa *et al.* (15)	Retrospective	Tunisia	92	2	50	8.62
Bastuji-Garin *et al.* (33)	Retrospective	Tunisia	198	4	36.7	6.70
Baican *et al.* (6)	Prospective	Romania	68	1.75	53	4.00
Kumar (32)	Prospective	India	13	2.33	37 (F), 58 (M)	4.40
Golusin *et al.* (34)	Retrospective	Serbia	51	1.55	55.6	6.60
Nanda *et al.* (27)	Retrospective	Kuwait	60	0.9	36.5	4.57
Langan *et al.* (3)[a]	Retrospective	UK	138	1.93	71	6.80
Michailidou et al, (14)[a]	Retrospective	Greece (Northern)	129	2.25	59.6	8.00
Chams-Davatchi *et al.* (17)	Prospective	Iran	1209	1.5	42	10.00 (Iran) 16.00 (Tehran)
Salmanpour *et al.* (31)	Retrospective	Iran (Southwestern)	221	1.33	38	6.70
V'lckova-Laskoska *et al.* (8)	Retrospective	Macedonia	133	1.33	52	4.40
Marazza *et al.* (10)	Prospective	Switzerland	7	2.5	62.3	0.60
Bertram *et al.* (9)[a]	Prospective	Germany (Lower Franconia)	41	-	62	0.50
Hahn-Ristic *et al.* (35)[a]	Retrospective	Germany (Lower Franconia, Mannheim)	14	1.33	-	0.98
Tallab *et al.* (26)	Retrospective	Saudi Arabia (Southern)	19	0.45	43.1	1.60
Micali *et al.* (13)	Retrospective	Italy (Eastern Sicily)	84	1.6	56	6.00
Mahe *et al.* (24)	Retrospective	Mali	30	4	46.7	2.90
Tsankov *et al.* (7)	Retrospective	Bulgaria (Sofia)	74	1.2	72.4	4.70
Bastuji-Garin *et al.* (12)	Retrospective	France	87	1.2	52	1.70
Hietanen *et al.* (11)	Retrospective	Finland	44	1.1	57.5	0.76
Simon *et al.* (25)	Retrospective	USA (Connecticut)	12	5	63.6	4.20 (non-Jewish) 32.00 (Jewish)
Pisanti *et al.* (16)[a]	Prospective	Israel (Jerusalem)	76	1.62	-	16.10
Uzun *et al.* (3)	Prospective	Turkey (Mediterranean)	148	1.35	43	2.40
Bozdag *et al.* (5)	Retrospective	Turkey (Aegean)	87	1.64	48	1.80
Yayli *et al.*	**Prospective**	**Turkey[b]**	**220**	**1.41**	**49.5**	**4.70**

* F: Female patients; M: Male patients
a. Studies including only patients with pemphigus vulgaris
b. Twenty provinces in different geographic regions

concomitant medications. Four patients (1.8%) had a family history of pemphigus.

DISCUSSION

This is the first study which aims to evaluate the rate of incidence of pemphigus in the Turkish population in the different geographic regions of Turkey. Thirty-three tertiary referral centers for blistering diseases in 20 different provinces from all 7 geographic regions of Turkey (8 centers from both the Central Anatolia and the Marmara, 6 centers from the Aegean, 5 centers from the Mediterranean, 3 centers from the Eastern Anatolia, 2 centers from the Black Sea, and 1 center from the Southeastern Anatolia regions) were included in this study to evaluate the rate of incidence of pemphigus in Turkey. As the study encompassed more than 60% of the Turkish population in 20 provinces from all geographic regions, lasted for one year prospectively, and involved 33 tertiary referral centers for the management of blistering disease, our results should therefore be reliable and realistic.

We found an incidence rate of 4.7 new cases per million people per year (95% CI 4.1-5.4). This incidence rate is nearly twice as high as previously reported in the Mediterranean region of Turkey by Uzun *et al.* (2.4 new cases per million people per year) as the first prospective epidemiologic data from Turkey (3). Additionally, a retrospective study from the Aegean region of Turkey had reported a lower incidence rate of 1.8 new cases per million people per year (5). The higher incidence rate of our study might be explained by the differences between the geographic

regions (the Mediterranean or the Aegean regions vs. all seven geographic regions of Turkey) and our broader study design, or by an increase in the rate of pemphigus incidence in Turkey. More precisely, our new incidence rate for Turkey is closer to reality, by covering the all Turkish regions and most of the Turkish population.

Several, mostly retrospective studies (Table 2) have been published on the incidence of pemphigus in different populations. The incidence of pemphigus in Turkey is similar to the countries of South-Eastern Europe such as Romania (6), Bulgaria (7), and Macedonia (8) (4, 4.4, and 4.7 new cases per million people per year, respectively) and higher than the ones in Central and Northern Europe, such as Germany (9), Switzerland (10), Finland (11), France (12) (0.50, 0.60, 0.76, 1.70 new cases per million per year, respectively). The incidence rate of pemphigus in our study is lower than the incidence in the countries around the Mediterranean Sea, such as Eastern Sicily (13), Greece (14), Tunisia (15), and Israel (16) (6.00, 8.00, 8.62, and 16.10 new cases per million people per year, respectively) and Iran (17) (10 new cases per million people per year).

The large variation in the incidence rate of pemphigus in different countries suggests the presence of various risk and predisposing factors including genetic background and environmental factors, such as foods or other lifestyle factors (18,19). Certain human leucocyte antigen (HLA) class II alleles are more prevalent in patients with pemphigus than in the general populations. Previous studies have demonstrated that HLA alleles DRB1*0402 and DQB1*0503 are positively associated with PV in multiple populations (20-22). These HLA antigens seem to have certain roles in the susceptibility to pemphigus through the development of an autoreactive T-cell response to desmogleins in patients carrying these haplotypes (23). It is notable that the incidence rate of pemphigus in Turkey is consistent with the geographical location of our country, between South-Eastern Europe and the Mediterranean area.

Regarding sex differences, there was a female predominance with a female/male ratio of 1.41 in our population. This observation is quite similar with most of the reported studies on pemphigus epidemiology. This ratio is generally between one and two, as in our study. In some studies, it even reaches four or five (24,25). Interestingly, the studies with male predominance with a female/male ratio of 0.45 and 0.9 were only reported in Saudi Arabia (26) and Kuwait (27), respectively.

The age of our patients ranged from 20-96. The overall mean age was 49.5 years. This finding is very similar with the data from the past 50 years reported in the studies from Macedonia (8), Romania (6), France (12), Tunisia (15), Taiwan (28), Mali (23), and Guadeloupe (29). The reported mean ages of the patients with pemphigus are generally higher in the studies from Central and Northern Europe (9,10,30) and lower in studies from Asian countries like Iran and India (17,31,32) (Table 2). According to common subtypes, the mean ages were 48.4 and 54.8 for PV and PF, respectively. Additionally, the mean ages of onset were 48.1 and 51.8 for PV and PF. In some endemic areas for PF such as Tunisia, the onset of the disease was much earlier, generally in the thirties especially in women, probably due to traditional lifestyle factors (12,33).

PV was the most common clinical subtype (192 patients, 87.3%) with a striking nine-fold higher incidence than PF in Turkish population. This result is very similar with the ratios of the studies from Mediterranean or Aegean regions of Turkey (3-5), 83.1% and 93.1%, respectively. These results in the Turkish population were also consistent with data of most of the reports from European, Mediterranean, or Asian countries. According to the results of some studies from mostly tropical regions like Tunisia (33) or Gaudeloupe (29), PF seems to be the most prevalent type of pemphigus. Interestingly, PE was reported as the most frequent subtype in Finland in an earlier study (11).

Regarding clinical characteristics, painful and persistent oropharyngeal erosions or ulcers were the presenting sign of the disease in most of the patients (54.1%). Additional mucosal involvements, including larynx involvement with hoarseness (35 patients, 15.9%), nasal involvement with bleeding (18 patients, 8.1%), and conjunctival involvement (17 patients, 7.7%) were observed mostly in patients with PV. The frequencies of those involvements in our study were remarkably higher than the results of the first prospective study of the Mediterranean region of Turkey (3). The mucocutaneous type of PV was the most frequent subtype (83 patients, 43.2%) in the PV group. The rate of mucosal PV (69 patients, 35.9%) was very close to that rate, in accordance to the well-known feature of the PV with mucosal onset.

The association of pemphigus with other diseases at the time of diagnosis was generally not investigated in other prospective studies. In our study, the most significant associated disease was hypertension (15 patients, 6.8%), and 13 patients (5.9%) were being treated with cardiovascular drugs, mostly angiotensin-converting enzyme inhibitors, at the time of diagnosis. Cardiovascular diseases and related medica-

tions were also the leading associations in the study from Switzerland (10) and Guadeloupe (29). Other associated diseases were diabetes mellitus in 5 patients and goiter, asthma and hyperlipidemia in 3 patients.

Our study had some limitations. Firstly, regarding recruitment, although 33 tertiary referral centers for blistering diseases in 20 different provinces from all 7 geographic regions of Turkey were included this one-year prospective study, we cannot be certain that we included all newly-diagnosed patients with pemphigus in this study period due to the fact that our study did not involve all the dermatology clinics in the entire country. The lack of a central registry for autoimmune blistering disease makes this impossible at present. However, considering the complex and life-threatening nature of the disease, cases may have been referred to our tertiary centers which are the main referral centers for blistering diseases in those regions. Because of this limitation, the incidence rate that we found may be defined as the minimal incidence rate of 4.7 per million people per year. Second, as a one-year prospective study and consistent with our main goals, we were not able to focus on the treatment of the patient and the rate of mortality among, which could be an important part of studies on pemphigus epidemiology.

CONCLUSION

The findings of this first nationwide epidemiologic study indicate that the rate of pemphigus incidence in Turkey is similar to the countries of South-East Europe, higher than those reported for the Central and Northern European countries, and lower than in the countries around the Mediterranean Sea and Iran. Considering the genetic and environmental factors predisposing to pemphigus, it may be interpreted as a result consistent with the geographical location of Turkey between South-Eastern Europe and the Mediterranean area.

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