Acta Dermatovenerol Croat 2014;22(4):246-249 ORIGINAL SCIENTIFIC ARTICLE

Epidemiology of Autoimmune Bullous Diseases and Therapeutic Modalities During a 10 Year Period in Iran

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Received: May 31, 2013
Accepted: September 1, 2014

SUMMARY Autoimmune bullous diseases are systemic disorders with autoantibodies that result in blisters. Aim of this study was to indicate the spectrum and treatment modalities of five types of bullous disorders most prevalent in the south of Iran: pemphigus vulgaris (PV), pemphigus foliaceus (PF), epidermolysis bullousa aquisita (EBA), bullous pemphigoid (BP), and pemphigoid gestationis (PG). Patients with PV, PF, BP, EBA, and PG were included in this study. The data regarding the age, sex, and the treatment used for PV, PF, and BP were recorded and analyzed in our center, a tertiary referral center. T-test and Mann-Whitney test for independent samples were used for the analysis of parametric and nonparametric variables, respectively. Chi-square test was used for frequencies. Of the 441 patients included in this study, 82.9% had PV, 4.7% PF, 8.5% BP, 1.5% EBA, and 1.3% PG. 93.5% of patients with PV, 95.3% with PF, and 100% with patients with BP were treated and responded to first line therapies with one or two medications.
The most frequent autoimmune bullous disease was PV, followed by PF. For PV and PF, combination of prednisolone and azathioprine was the most frequent first line medication. In the patients with BP, prednisolone monotherapy was the most frequent one. Only a minority of patients with PV and PF needed the third or fourth medications.

KEYWORDS: pemphigus vulgaris; pemphigus foliaceus; bullous pemphigoid; treatment

INTRODUCTION

Autoimmune bullous disorders (ABD) are a group of systemic disorders with autoantibodies that result in intraepidermal and subepidermal blisters (1). They need serious medical care, otherwise they have relatively high mortality (2,3).

Limited research has been done worldwide on the epidemiology and treatment of ABD. In particular, only a small number of epidemiological studies are available about epidemic spectrum and treatment of various types of ABD in Iran.

The aim of this study was to indicate the spectrum of five types of most prevalent bullous disorders in the south of Iran. We also determined the frequency of different types of ABD treatment.

PATIENTS AND METHODS

During a 10 year period, the records of all the new patients admitted with bullous disease at Shiraz University of Medical Sciences (SUMS) dermatology center were evaluated. This is the major tertiary referral

Acta Dermatovenerol Croat
2014;22(4):246-249

center for dermatologic diseases in the south of Iran. Private dermatologists also refer new bullous disorder patients to our tertiary center for better management and follow up. The diagnosis was made based on the clinical presentation, histopathology, and direct immunofluorescence.

Five diseases were included in our study: pemphigus vulgaris (PV), pemphigus foliaceus (PF), epidermolysis bullousa aquisita (EBA), bullous pemphigoid (BP), and pemphigoid gestationis (PG). The data regarding the age, sex, and the treatment used for PV, PF, and BP were recorded and analyzed.

The SPSS statistical package was used for analysis. T-test and Mann-Whitney test for independent samples were used for all parametric and nonparametric variables analysis, respectively. Chi-square test was used for qualitative variables. In all statistical tests, $P<0.05$ was considered significant.

RESULTS

About 6400 patients with various dermatologic diseases were admitted during the 10 year period of the study. A total number of 441 patients with autoimmune bullous disorders were included. 369 cases were diagnosed as PV (82.9% of the total cases). Table 1 shows characteristics of different bullous diseases including the number, frequency, mean age, median age, age range, and sex ratio.

We studied different medical treatments used in our center for treating PV, PF, and BP. Out of the 369 cases of PV, there were only 311 patients with available treatment data. The frequency of the 1st, 2nd and 3rd line therapies for the cases are shown in Table 2 and 3.

93.5% of patients with PV, 95.3% with PF, and 100% of patients with BP responded to the 1st line therapies of one or two medications. 6.5% of patients with PV and 4.7% with PF needed the 2nd and 3rd line therapies in order to control the disease.

DISCUSSION

ABDs are rare blistering diseases affecting the skin and mucosa. Their clinical and epidemiologic features vary according to geographic location and ethnic background. Few surveys have been done to describe the spectrum of ABD in our region. The SUMS dermatology center is the referral center for dermatology diseases for southern Iran, with about 6.5 million inhabitants in this area.

Epidemiology

441 ABD cases were included in the study. PV accounted for the majority of cases (83.67%), followed by BP, PF, EBA, and PG. PV outnumbered other ABD cases; this finding is similar to studies conducted in most of the world, except Latin American counties, Mali, Tunisia and Finland: in these regions, other bullous diseases such as fogo selvagem, PF, and pemphigus erythematosus predominate (3-8).

Patients with PV and PF were predominantly men. This is in contrast to what has been noted in Germany, Kuwait, Switzerland, and the UK (9-12); studies from India, Saudi Arabia, Bangladesh, and China found the same predominance (13-16). Patients with BP were predominantly women, in line with previous studies (2,10,11). However, studies from China and Germany found that patients with BP were predominantly men (15,16). On the other hand, patients with EBA were also predominantly women in our study, as in Kuwait (11), but a study of north of Iran reports a male predominance (3).

The mean ages were 45.8 years for PV, 40.4 years for EBA, and 50.7 years for PF. The mean ages for PV and EBA are similar to what was found in the studies in the north of Iran, Saudi Arabia, and Singapore (3,13,17). PF mean age is relatively close to Korea and Japan, where the disease presented in the sixth and seventh decades (18,19). The mean age of patients with PG was 27.3 years, which is younger than that of the study from Sao Paulo (30.3 years) (20).

Table 1. The frequency and epidemiology of autoimmune bullous disease during a 10 year period

M : F ratio	Age range (years)	Median of age (years)	Mean ± SD of age at onset (years)	% of patients	No. of patients	Autoimmune bullous disease
1.1 : 1	21-89	44	45.8 ± 16.2	83.67	369	Pemphigus vulgaris
1.1 : 1	22-75	51	50.7 ± 17.35	4.76	21	Pemphigus foliaceus
1 : 1.23	21-90	65	64.1 ± 17.70	8.61	38	Bullous pemphigoid
1 : 1.2	17-69	41	40.4 ± 17.82	1.58	7	Epidermolysis bullousa aquisita
All were females	19-35	27	27.3 ± 5.32	1.36	6	Pemphigoid gestationis

Table 2. The frequency of the first line therapies in autoimmune bullous disease in our center

Dx/drug% (No.)	Prednisolone	Dapsone	Prednisonlone +cyclosporine	Prednisolone+ azathioprine	Prednisolone+ MM	Prednisolone+ dapsone
PV (291)	18.6% (58)	–	0.9% (3)	68% (212)	4.5% (14)	1.2% (4)
PF (20)	38% (8)	–	–	47.6% (10)	–	9.5% (2)
BP (38)	50% (19)	5.2% (2)	–	26.3% (10)	–	18.4% (7)

DX: disease; PV: pemphigus vulgaris; PF: pemphigus foliaceus; BP: bullous pemphigoid; MM: mycophenolate mofetil

BP was the second most common ABD in this study, PV being the most common. The ratio of PV to BP was 9.7:1, which is close to the results from studies in the north of Iran, Kuwait, and China (11,15). The median age for BP was 65 years, which is similar to the results of the study of the north of Iran (59.4 years) (3).

EBA was observed in 1.5% of patients, and PG accounted for 1.3% of patients. Both estimates are higher than what was reported in the north of Iran (0.5% and 0.7%, respectively) (3).

Treatments

Prednisolone with the dosage of 0.5 to 1.5 mg/kg is the first line medication that is used for ABD, and steroid sparing agents are added in an attempt to taper corticosteroids. For PV and PF, the combination of prednisolone and azathioprine was the most frequent first line medication with 68% and 47.6%, respectively. It was followed by monotherapy with prednisolone accounting for 18.6% and 38% in PV and PF, respectively.

In the BP group, prednisolone monotherapy (50%) was the most frequent medication, followed by prednisolone in combination with azathioprine (26.3%). Dapsone was used more frequently (23.6%) in BP patients compared to PV and PF (1.2% and 9.5%, respectively). Prednisolone in combination with mycophenolate mofetil (1.2%) or cyclosporine (0.9%) was used as the first line therapy in a minority of PV cases.

The patients who did not respond to the first line medications were treated with the 2nd and 3rd line therapies. None of BP cases required the third line medication. Only a minority of PF patients (4.7%) needed the addition of the third medication, in which only the combination of prednisolone, azathioprine, and mycophenolate mofetil was used.

In the PV group, the most commonly used third line medications were dapsone (2.9%), mycophenolate mofetil (1.6%), or cyclosporine (0.9%). The combination of prednisolone with mycophenolate mofetil and tacrolimus was used in 0.3% of patients, which was similar to the frequency of using the combination of prednisolone with cyclophosphamide and dapson (0.3%).

Only 0.3% of PV cases received the four drug combination of prednisolone, azathioprine, mycophenolate mofetil, and dapson.

The more frequent use of the third and fourth medications in PV may imply the more severe nature of PV. In the study performed in Germany, more than 50% of patients with PV received prednisolone as the first medication and azathioprine was added in 81% of cases, which is close to our results. In that study, azathioprine was added in 69% of patients with BP, which is higher than the findings of our study (26.3%). Immunosuppressive agents that were used as alternative were similar to those used in our center (21).

CONCLUSION

The present study was carried out in a tertiary referral center. Although most of ABD cases are referred to tertiary centers, the milder cases might be managed in an outpatient setting and would not have been included in this study. Due to the retrospective nature of this study, we could not determine the exact time of the patients' response to the medications.

Table 3. The frequency of 2nd and 3rd line therapies for autoimmune disease in resistant cases

Dx/drug % (No.)	Prednisolone+ azathioprine+ dapsone	Prednisolone+ azathioprine+ MM	Prednisolone+ azathioprine+ cyclosporine	Prednisoloe+ MM+tacrolimus	Prednisolone+ cyclophospmide+ dapsone	Prednisolone+ azathioprine+ MM+dapsone
PV (20)	2.9% (9)	1.6% (5)	0.9% (3)	0.3% (1)	0.3% (1)	0.3% (1)
PF (1)	–	4.7% (1)	–	–	–	–

DX: disease; PV: pemphigus vulgaris; PF: pemphigus foliaceus; MM: mycophenolate mofetil

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