Acta Dermatovenerol Croat 2005;13(4):228-232 CLINICAL ARTICLE

Epidemiology of Acquired Bullous Diseases in Eastern Croatia: A Retrospective Prewar to Postwar Study

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Received: April 1, 2004
Accepted: October 14, 2005

SUMMARY The purpose of this study was to evaluate the epidemiology of bullous diseases (BD) in eastern Croatia during a ten-year period (1986-1990/1992-1996), and to estimate the effect of prolonged exposure to traumatic events during the war in Croatia on the prevalence and incidence of acquired BD. The files of all BD patients hospitalized at Department of Dermatology and Venereology, Osijek University Hospital, during the periods from January 1986 to December 1990 and from January 1992 to December 1996 were collected and analyzed with regard to personal data, history of the disease including age, sex and onset of symptoms, clinical diagnosis, laboratory findings, and associated illness. Forty-five patients were newly diagnosed with BD over the ten-year period. During the 1986-1990 period, 19 patients with BD represented 0.89% of 2133 patients admitted to our Department. During the 1992-1996 period, 26 newly diagnosed patients with BD represented 1.27% of 2050 patients treated at our Department. Females were more affected than males. The most common clinical variant was pemphigus vulgaris, occurring frequently in the middle-aged population. All our patients were exposed to prolonged stressful war conditions during the 1992-1996 period, therefore, we speculate that extended emotional stress may have triggered the onset of the disease.

KEY WORDS bullous skin diseases; epidemiology; war; eastern Croatia

INTRODUCTION

Pemphigus and other acquired bullous diseases (BD) are autoimmune blistering disorders that affect the skin and mucous membranes. The family of acquired bullous diseases includes the group of pemphigus diseases (pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus brasiliensis, pemphigus erythematosus, paraneoplastic pemphigus, IgA pemphigus and pemphigus herpetiformis), and the group of pemphigoid diseases (pemphigoid bullosus, dermatitis pemphigoides mucocutanea chronica, pemphigoid gestationis, dermatititis herpetiformis Duhring, IgA pemphigoid and epidermolysis bullosa acquisita) (1). The group of pemphigus diseases is characterized by intraepidermal blisters due to the loss of cell-cell adhesion of keratinocytes, and immunopathologically by the finding of mostly pathogenic IgG, and rarely IgA autoantibodies directed against the cell surface of keratinocytes (2,3). The most common type in this group is pemphigus vulgaris, which is caused by autoantibodies against desmogleins 1 and 3 (1). The pemhigoid group includes

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a series of chronic diseases with subepidermal blisters, the most common type being pemphigoid bullosus. Antibodies are directed against various components of the basement membrane zone (1). Dermatitis herpetiformis, by recent classification included in the pemphigoid group, is a chronic, intensely pruritic, clinically polymorphic dermatitis with characteristic IgA deposition in the dermal papillae (1).

The genetic background alone, though essential, is not by itself sufficient to initiate the autoimmune response, as proven by the reports of pemphigus in only one of two monozygotic twins (4) and only two of three siblings with identical predisposing haplotype (5). The intervention of inducing or triggering factors seems to be crucial to set off the full-blown disease (6). Interactions between the nervous system and the immune system have been demonstrated (7); thus, it was suspected that this interaction could contribute to the onset of several autoimmune diseases, including pemphigus. Previous reports of a few cases suggest that the onset of bullous disease might be triggered by psychological stresses (8,9). The other common factors involved in the pathogenesis of pemphigus are infections (10), exposure to pesticides and gardening materials, occupational exposure to metal vapor, cigarette smoking, certain drugs, and environmental conditions such as excessive heat and humidity (11).

Pemphigus is a disease showing an uneven geographical distribution. It is currently thought to be much more common in midlatitude, subtropical and tropical climates. Thus, in Finland, the annual incidence of pemphigus is extremely low, 0.076 per 100,000 population (12); in North America it is 0.29-0.42/100,000 adults (13); and in Malaysia, 0.2/100,000 (14).

The aims of our study were to establish the incidence of acquired BD among hospitalized patients in eastern Croatia, and its distribution according to sex, age of onset, clinical diagnosis, laboratory findings and occupation during two periods. In addition, we wanted to estimate whether prolonged exposure to stressful conditions during the war in eastern Croatia influenced the prevalence and incidence of acquired BD.

PATIENTS AND METHODS

We collected and analyzed the files of all patients with bullous dermatitis hospitalized at Department of Dermatology and Venereology, Osijek University Hospital, Osijek, Croatia during two periods: before the war (from January 1986 to December 1990), and after the war (from January 1992 to December 1996). It should be emphasized that during the prewar period, our Hospital had a far greater catchment area that included east Croatian regions (Slavonia, Baranya and Vukovar with its surroundings), whereas during the postwar period the region was mostly occupied by Serbian military forces, thus the number of patients admitted to our department being considerably smaller.

The diagnosis of BD was based on the following criteria: (a) clinical examination, skin bullae and/or mucous membrane erosions; (b) histologic, acantholysis revealed by routine biopsy examination and Tzanck's smear; and (c) *in vivo* deposited or circulating specific antibodies on direct and indirect immunofluorescence. Direct immunofluorescence was only performed in three patients because we had technical problems (sending materials to Zagreb) due to the war conditions in eastern Croatia. Furthermore, it was not possible to establish the annual incidence of BD in the general population in eastern Croatia after the war because of the considerable population migration in the region.

Data were analyzed using Student's t-test. The level of significance was set at $p<0.05$.

RESULTS

During the 1986-1990 and 1992-1996 periods, 4183 patients were treated at Department of Dermatology and Venereology, Osijek University Hospital. We diagnosed 45 patients with bullous dermatitis, accounting for 1.08% of the total number of admitted patients. During the 1986-1990 period, 19 patients with BD accounted for 0.89% of 2133 patients admitted to our Department. During the 1992-1996 period, 26 newly diagnosed patients with BD accounted for 1.27% of 2050 patients treated at our Department (Table 1). Although a greater number of BD patients were diagnosed in the postwar period, the difference was not statistically significant ($t=0.47$, $p=0.645$). Nevertheless, it is important to emphasize the increased incidence of BD (2.56%) in 1992, immediately after the war had begun in eastern Croatia, as compared with the lower prewar incidence (0.85%) recorded in 1990.

We analyzed patient distribution according to sex and age at disease onset during the 1986-1990 period. The majority of patients were aged 50-59 (n=5, 33.3%) and 40-49 (n=3, 26.7%) (Fig. 1), with a marked female predominace (F/M ratio 2:1).

Patient distribution according to sex and age at disease onset during the 1992-1996 period is shown in Figure 2. Most patients were aged 40-49

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Table 1. Distribution of bullous diseases patients during two time periods

Prewar (1986-1990)				Postwar (1992-1996)			
Year	Total number of hospitalizations	Patients with bullous diseases		Year	Total number of hospitalizations	Patients with bullous diseases	
		No	%			No	%
1986	405	7	1.73	1992	117	3	2.56
1987	412	2	0.49	1993	226	5	2.12
1988	343	0	0.00	1994	416	8	1.92
1989	501	6	1.20	1995	743	6	0.81
1990	472	4	0.85	1996	548	4	0.73
1986-1990	2133	19	0.89	1992-1996	2050	26	1.27
1986-1996	4183	45	1.08				

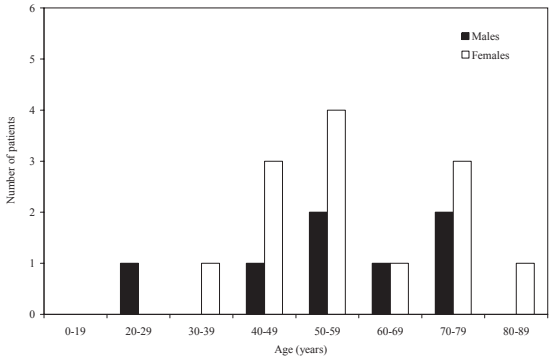

Figure 1. Patient distribution according to sex and age at disease onset (1986-1990)

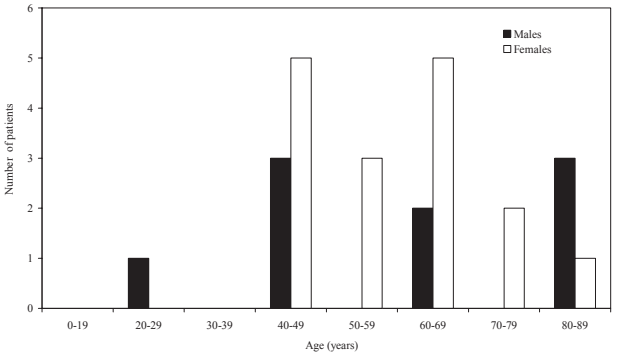

Figure 2. Patient distribution according to sex and age at disease onset (1992-1996)

(n=6, 37.5%), followed by those aged 50-59 and 60-69 (n=3 each, 18.8%), also showing a female predominance (F/M ratio 2.2:1). The youngest patient was a 22-year-old male.

According to clinical features, during the 1986-1996 period, pemphigus group included 29 (64.4%) and pemphigoid group 16 (35.6%) patients (Table 2). The most common clinical feature in pemphigus group was pemphigus vulgaris, diagnosed in 28 (59.6 %) patients, whereas one (2.1%) patient had pemphigus foliaceus. Histopathologic findings were positive in 40 (85%) patients; direct immunofluorescence was positive in two (7%) patients and negative in one patient. Indirect immunofluorescence was positive in 26 (55%) and negative in 19 (40%) patients.

The first manifestation of the disease most frequently occurred in December (n=8, 17.0%), and quite rarely in November (n=1, 2.1%) (Fig. 3).

The majority of patients were retirees (n=19, 42.3%), housewives (n=10, 22.2%), and workers (n=10, 22.2%) (Table 3). Interestingly, in the group of employed patients, none had high education.

We treated 25 (55.6%) patients with corticosteroid therapy, 17 (37.8%) patients with a combination of corticosteroid and immunosuppressive therapy, two patients with dapsone, and one patient with gold salts.

Malignant disease was diagnosed in four pemphigoid group patients: facial basal cell carcinoma, cervical carcinoma, lingual and retromolar area carcinoma, and colon carcinoma. During the next 5-year period, we followed-up all 45 patients; three of those from pemphigoid group died from malignant disease, five died from old age, and one woman in pemphigus group died from cardiac arrest.

DISCUSSION

While the etiology of pemphigus is still unknown, several factors have been implicated for its variable geographic, ethnic and genetic background, an as yet unidentified infectious “agent”, excessive heat, solar radiation, dietary habits, pregnancy (11), and psychological stress (8). In our study, we investigated the incidence and distribution of BD in eastern Croatia during the prewar 1986-1990 period and postwar 1992-1996 period, according to clinical diagnosis, sex, age at onset, and occupation. We also investigated if strong emotional and psychological distress such as war trauma, displacement, loss of home, or death of family members had an impact on the incidence of BD in our population.

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Table 2. Distribution of bullous diseases patients according to sex and diagnosis

	Prewar (1986-1990)			Postwar (1992-1996)			1986-1996
	Male	Female	Total	Male	Female	Total	Total
Pemphigus group	4 (66.7%)	10 (76.9%)	15 (75.0%)	5 (55.6%)	10 (58.8%)	16 (59.3%)	29 (64.4%)
Pemphigoid group	2 (33.3%)	3 (23.1%)	5 (25.0%)	4 (44.4%)	7 (41.2%)	11 (40.7%)	16(35.6%)
Total	6 (100%)	13 (100%)	20 (100%)	9 (100%)	17 (100%)	27 (100%)	45 (100%)

During the 1986-1990 period, we diagnosed 19 patients with BD, accounting for 0.89% of 2133 patients admitted to our Department. During the 1992-1996 period, 26 newly diagnosed patients with BD represented 1.27% of 2050 patients treated at our Department. Although the number of newly diagnosed patients was higher in the postwar period, there was no statistical significance compared to the number of patients diagnosed in the prewar period. This could be explained by the fact that a great part of eastern Croatia was still occupied during the 1992-1996 period, therefore a considerable number of the population emigrated to different parts of Croatia and Europe. However, there was an increased incidence of BD (2.56%) during the year 1992, immediately after the war had begun in eastern Croatia, as compared to a lower prewar incidence (0.85%) during 1990. According to sex, in Mediterranean and midlatitude climates, pemphigus affects women more than men (15-17), which was confirmed by our results. Pemphigus vulgaris is the most common clinical variant of the disease in eastern Croatia, as has been reported in other epidemiological studies (16-18). According to literature data, pemphigus affects primarily middle-aged persons (12,16,18), as also shown in our study where the majority of patients were aged 40-59. The greatest number of patients were retirees and housewives.

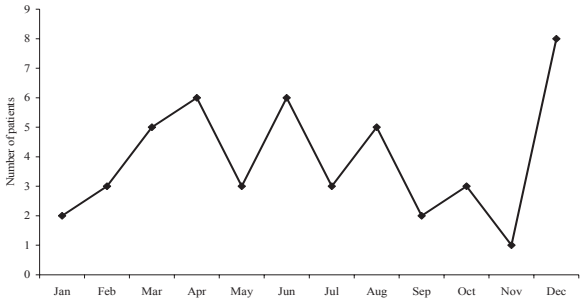

Figure 3. Patient distribution according to months of the year (1986-1996)

There are only few reports on stress-induced pemphigus (8,9,19). Cremniter *et al.* found 12 of 13 patients to have experienced a stressful life event such as close relative's or husband's death during the year preceding the onset of pemphigus (9). To our knowledge, the role of severe stressful events such as war has not yet been investigated. We diagnosed a greater number of patients with BD in eastern Croatia during the 1992-1996 period, when there still were war operations in this part of the country. Also, in this period BD affected younger patients. Some authors found a low incidence of pemphigus during the war in Croatia (1991-1995), which almost doubled from 1996 to 1998 (17).

In conclusion, we found a higher incidence of acquired BD in eastern Croatia during and immediately after the war. All our patients were from the war affected region, and showed a disease onset at an earlier age. Therefore, we speculate that prolonged emotional and psychological stress could have triggered the onset of BD in our region.

Table 3. Distribution of 45 patients according to occupation

	Prewar (1986-1990) n= 19		Postwar (1992-1996) n= 26		Total No of patients 45
	Male	Female	Male	Female	Total
Housewife	0 (0.0%)	7 (53.8%)	0 (0.0%)	3 (17.6%)	10 (22.2%)
Retired	5 (83.3%)	2 (15.4%)	3 (33.3%)	9 (53.0%)	19 (42.3%)
Unemployed	0 (0.0%)	0 (0.0%)	3 (33.3%)	3 (17.6%)	6 (13.3%)
Worker	1 (26.7%)	4 (30.8%)	3 (33.3%)	2 (11.8%)	10 (22.2%)
Total	6 (100 %)	13 (100%)	9 (100%)	17 (100%)	45 (100%)

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