

Pemphigus in Israel – An Epidemiologic Analysis of Cases in Search of Risk Factors

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Abstract

Background: Despite the high incidence of pemphigus in the Jewish population, data on the epidemiology and etiology of the disease in Israel are sparse.

Objective: This study was conducted to identify clinical and epidemiologic features of pemphigus patients in Israel, while searching for risk factors that induce or exacerbate the disease.

Methods: Demographic and clinical information was recorded from the charts of 55 pemphigus patients treated over a 5 year period. A sample of 22 patients was compared to 22 age and gender-matched controls by means of a questionnaire querying details on lifestyle, including occupation, diet, sun exposure, and smoking.

Results: The findings show that the typical Israeli pemphigus patient is middle-aged, married, and of East European or Middle Eastern origin. The most common diagnosed clinical variant was pemphigus vulgaris, followed by pemphigus erythematosus. Some 70% of patients were treated with two or more immunosuppressive drugs and 62% entered long-lasting remission. Twenty-three percent of patients were exposed through their work to chemical substances, mainly pesticides, at the beginning of the disease and 18% of patients were continually exposed to ultraviolet radiation 5 years prior to onset of the disease.

Conclusions: There is a possible correlation between occupational exposure to pesticides and UV radiation, and pemphigus induction.

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The uneven geographic distribution of pemphigus can be roughly classified into a western world type where pemphigus vulgaris predominates, and a developing world variant in which the superficial pemphigus group, pemphigus foliaceus, is more common and patients are younger [1]. The annual incidence in North America, Europe and Israel ranges from 0.5 to 1.6 new cases per 100,000 inhabitants [2]. In Brazil, pemphigus foliaceus is endemic and reaches rates of 2.5% annually in children and young adults. Data accumulated in the last decade from the developing world, in particular India [3], Africa [4] and the Arabian Peninsula [5–7], show a high incidence with the clinical features of pemphigus foliaceus.

Despite the well-established high incidence among Jews and the varied ethnic origins of the Israeli population, detailed epidemiologic data are lacking for this country. Two main studies were performed: one [8] in the 1970s reported an annual incidence of 1.6 per 100,000 adults in Jerusalem over a 20 year period, with high

morbidity in Ashkenazi (of central and Northern European origin) females and adults over 40 years of age. The second report, a retrospective survey carried out in the late 1980s covering 16 years in the Sharon and Dan regions (the central coastal plain), turned up 140 patients. Pemphigus vulgaris was the most common type, and again, most patients were of Ashkenazi origin, although there was also a high percentage of individuals of Middle Eastern and Sephardic (North African) origin [9].

The present study examines the clinical features, clinical course and prognosis of pemphigus patients in Israel, and attempts to identify risk factors for developing the disease.

Patients and Methods

The files of 55 pemphigus patients treated in the outpatient dermatology departments of Tel Aviv Sourasky Medical Center, Sheba Medical Center (Tel Hashomer) and HaEmek Medical Center (Afula) from 1992 to 1997 were reviewed for demographic information, history of the disease, symptoms, clinical diagnosis, associated illness, drug intake, therapy and remission. A random sample of 22 of these patients was compared with 22 healthy matched controls by means of a detailed questionnaire that gathered information on smoking, diet, occupation, sun exposure, emotional stress, and other lifestyle items. Ultraviolet radiation exposure was categorized into occupation and leisure time, and the quantity in years of cumulative exposure. Occupation was classified into indoor versus outdoor work, and further into jobs involving handling of chemicals such as factory work, construction, agriculture, art and photography. With regard to diet, patients were asked about consumption of vegetables such as garlic and onions, fruits like mango and figs, various seeds, spices for meat and salad, tea, coffee, cola and wine.

Statistical analyses were carried out using Student's *t*-test for continuous variables, and the chi-square test for categorical variables. Fisher exact test was performed when the number of observations was less than 5.

Results

The 55 pemphigus patients ranged in age from 20 to 92 years, mean 61 years, SD 18.38. The 22 age, gender and origin-matched controls were gathered from outpatient clinics in the hospitals. Demographic and clinical data on the 55 patients are summarized in Table 1. The mean age of disease onset was 54 ± 18.38 years. Pemphigus vulgaris was the most common clinical type, followed by pemphigus erythematosus. Mucosal erosions were the most

UV = ultraviolet

Table 1. Demographic and clinical data on the 55 pemphigus patients

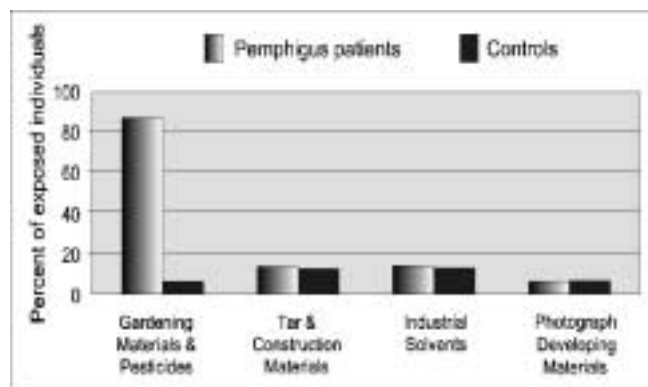
Item	Number (percentage of total)
Men	22 (40%)
Women	33 (60%)
Age	61 ± 18.38 years
Family status	
Single	9 (17%)
Married	38 (71.7%)
Widow	6 (11.3%)
Place of origin	
Eastern Europe	26 (47.3%)
Middle East	25 (45.5%)
Asia	3 (5.55%)
Africa	1 (1.8%)
Type of pemphigus	
Vulgaris	45 (81.8%)
Erythematous	4 (7.3%)
Foliaceous	3 (5.5%)
Vegetans	2 (3.6%)
Age of onset	54 ± 4.96 years
Presenting signs	
Blisters	29 (52.7%)
Erosions	43 (78.2%)
Crusts	9 (16.4%)
Other	9 (16.3%)
Distribution	
Skin	15 (27.3%)
Mucosae	18 (32.75%)
Skin and mucosae	22 (40%)
Mucosal involvement	
Oral	38 (92.7%)
Genitoanal	5 (7.3%)
Sun exposure distribution	
No	7 (19.4%)
Yes	14 (38.9%)
Partial	15 (41.7%)

Table 2. Comparative lifestyle data in patients and controls

	No. of patients	No. of controls	P value
Men	8	13	0.05
Women	14	9	NS
Age	64 ± 18.38	52 ± 19.35	NS
Smoking	6	9	NS
Occupational exposure to chemicals	13	1	0.001
Occupation exposure to UV radiation	10	2	0.01
Spicy diet	15	6	0.11
Emotional stress	7	5	NS

common presenting sign. Lesion distribution favored sun-exposed areas in 42 patients (80%). One-third of the patients lived in rural areas, whereas almost all of the controls lived in urban areas.

The majority of patients (67%) were treated with a combination of immunosuppressive drugs, mainly systemic corticosteroids and

**Figure 1.** Contact with chemicals among the 55 pemphigus patients.

azathioprine, and more than half (62%) were in clinical remission and off systemic therapy at the time the study was conducted in 1997.

A comparison of lifestyle parameters in patients and controls are summarized in Table 2. The statistically significant differences between the 22 sample patients and the 22 controls were related to occupation. At the time of disease onset about one-fourth of the patients (23%) were in a place or occupation that exposed them to specific chemical substances, compared to only 5% of controls. Pesticides and gardening materials were the most prominent offending agents [Figure 1]. Of the 22 sample patients, 18% were exposed through jobs to UV light, with a mean of 5 years from the beginning of exposure to the onset of disease.

Another significant finding was the high usage of spices in the patients' diets compared to those of controls (71% and 33%, respectively). No conclusions could be drawn about any specific items because of the large number and variety of condiments, which included several types of tea leaves, seeds, and the like.

Lifestyle parameters not found to be of statistical importance were emotional stress, associated illness, drug intake, pregnancy, and hormonal intake. Smoking was less frequent among pemphigus patients (30% and 38%, respectively) than controls, but the small sample size prevents drawing any conclusion from this finding.

Discussion

This retrospective controlled study delineates some of the features of the typical Israeli pemphigus patient: middle-aged, married, of East European or Middle Eastern origin. In line with the usual descriptions of the disease, mucocutaneous erosions were the most frequent finding. Prognosis was relatively benign, with disease control and long remissions after initiating therapy in 62% of patients.

Our findings concur with previous studies regarding the growing proportion of people of Middle Eastern and North African origins among pemphigus patients, a fact that has not been addressed in the literature. The epidemiologic pattern in Israel fits the reports of high incidence of the disease in Greece, Bulgaria and other countries of the eastern Mediterranean Sea; they may represent a focus of population with high susceptibility to pemphigus in this region.

The finding that pemphigus vulgaris was the most common type, followed by pemphigus erythematosus, may be related to the abundant sunlight in Israel, which is encountered in neighboring countries where this pattern is seen as well.

The past decades have seen tremendous progress in biomolecular research on the autoimmune process in pemphigus, and most of the involved antigens have been traced. There are, however, no unequivocal conclusions regarding the etiology of the disease. The prevailing concept is that pemphigus stems from a combination of endogenous and exogenous factors in genetically susceptible individuals [10,11]. The exogenic factors are numerous and include drugs [12], UV radiation [13], stress [14], infection [12,15,16], hormones [17], and others [13,18].

The results of the present study indicate a correlation between present and past occupation and pemphigus. The jobs of most of the patients exposed them to chemical substances, the most prominent being pesticides and gardening materials. Moreover, one-third of the patients lived in a rural setting at the onset of their disease, where exposure to pesticides is greater than in the city.

Krain [19] reported the first series of 14 cases that developed pemphigus following occupational contact with various chemical substances, gardening materials and pesticides being the most incriminated. Since that report, case studies of pemphigus induction by phosphamides, chrome salts [20], pentachlorophenol [21] and other agents continue to appear in the literature.

Pesticides are widely used in Israel for agricultural and domestic purposes. The chemical compounds vary and have changed over the years. In the 1960s the organochlorines were common – lindane, endosulphan, DDT, benzohexachloride. While all but endosulphan have been outlawed in Israel because of their toxicity, the Palestinian Authority continues to use them [22]. Since the 1970s Israel has used mainly organophosphate pesticides for cotton, oranges, vegetables, flowers and water sources. Phenol and nitrous compounds are used for sterilizing barns and pens [23].

There are several mechanisms that could explain how pesticides are involved in pemphigus pathogenesis. Many of them can cause a direct toxic effect to desmosomes, while others activate the immune system, specifically the T helper-2 arm with its array of cytokines, generating autoantibodies [24]. A recent hypothesis holds the acetylcholine receptor, a surface protein and a molecule altered by different pesticides, as also being a target of pemphigus antibodies [25].

Our study also revealed that some 40% of the patients had been continuously exposed to UV radiation in their work 5 years prior to developing the disease. The distribution of lesions on sun-exposed areas and the high prevalence of pemphigus erythematosus type support these findings. Again, the question is whether the mechanism is simply a phototoxic effect or entails a specific immunomodulatory process.

Our findings on the epidemiologic features related to pemphigus in the genetically susceptible Jewish population living in this geographic region indicate possible risk factors that cannot be dismissed as merely incidental. They need to be investigated in other ethnic groups residing in Israel and neighboring countries, and in *in vitro* molecular studies.

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