



# Remarkable differences in the epidemiology of pemphigus among two ethnic populations in the same geographic region

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**Background:** The epidemiology of pemphigus in different ethnic populations exposed to similar environments is unknown. Trends in the incidence of pemphigus based on an immunopathologically validated cohort have not been investigated.

**Objectives:** We sought to estimate the incidence of pemphigus in Israel and to investigate differences between the 2 major ethnic populations.

**Methods:** Pemphigus incidence was retrospectively estimated from January 2000 to December 2015 in 2 Israeli regions with a total population of 1.56 million inhabitants.

**Results:** One hundred eighty patients with pemphigus (mean age,  $54.70 \pm 16$  years) were identified. The overall estimated incidence was 7.2 per million inhabitants per year (95% confidence interval, 6.2-8.3). The incidence in the Jewish population was threefold higher than that in Arabs (9.6 vs 3.2 cases per million per year, respectively;  $P < .0001$ ) and higher among women than men (9 vs 5.3 cases per million per year, respectively;  $P < .0001$ ). The incidence decreased from 8.4 cases per million per year in 2000 to 2005 to 7.0 and 6.0 (95% confidence interval, 4.5-7.9) in 2006 to 2010 and 2011 to 2015, respectively ( $P = .068$ ).

**Limitations:** This study was limited by the retrospective design and the small population.

**Conclusions:** The incidence of pemphigus in Israel is among the highest reported worldwide and is significantly more frequent among Jews. (J Am Acad Dermatol 2016;75:925-30.)

**Key words:** Arabs; epidemiology; ethnicity; foliaceus; HLA; Jews; pemphigus; vulgaris.

## INTRODUCTION

Pemphigus is a rare, chronic, potentially life-threatening autoimmune blistering disease of the skin and mucous membranes. There are 2 major subtypes of pemphigus: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). The etiopathogenesis

### Abbreviations used:

DIF: direct immunofluorescence  
Dsg: desmoglein  
IIF: indirect immunofluorescence

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Funding sources: None.

Conflicts of interest: None declared.

Accepted for publication June 18, 2016.

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Published online September 7, 2016.

0190-9622/\$36.00

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<http://dx.doi.org/10.1016/j.jaad.2016.06.055>

of pemphigus is characterized by acantholysis and intraepidermal blister formation resulting from immunoglobulin G (IgG) autoantibodies directed against desmoglein 3 (Dsg3; PV) and Dsg1 (PF), two transmembrane desmosomal glycoproteins.<sup>1,2</sup>

Pemphigus shows an uneven geographic and ethnic distribution. The incidence of PV is variable and ranges from 0.76 per million individuals per year in Finland<sup>3</sup> to 16.1 per million individuals per year in Jerusalem.<sup>4</sup> PF is less common in most populations, and the estimated incidence ranges from 0.5 per million individuals per year in Western Europe<sup>5</sup> to 6.7 per million individuals per year in Tunisia.<sup>6</sup> Interestingly, a high incidence of pemphigus was observed in some ethnic groups, namely Ashkenazi Jews and those of Mediterranean origin. This observation has been shown to be strongly related to several human leukocyte antigen (HLA) class II genes—HLA-DRB1\*04 and HLA-A\*10—that have been more frequently found among Ashkenazi Jewish patients with pemphigus.<sup>7-10</sup> However, population-based studies have not addressed differences in the epidemiology of pemphigus among genetically distinct ethnic groups that have been exposed to a similar environment. In addition, trends in the incidence of pemphigus based on an immunopathologically validated cohort over a long duration of time have not been previously reported.

The objective of our study was to estimate trends in the incidence of pemphigus in northern Israel from 2000 to 2015 in relation to the major ethnic groups who inhabit the same geographic area and are therefore exposed to a similar environment. A systematic validation of cases using clinical, histologic, and immunological criteria for pemphigus was performed.

## METHODS

### Study population

To assess trends in the incidence of pemphigus over a 16-year period, we conducted a retrospective population-based study from January 2000 to December 2015 in 2 Israeli regions: Haifa and the northern districts, populated with 875,000 and 691,000 people, respectively, corresponding to a combined population size of 1.567 million inhabitants according to the 2008 census.<sup>11</sup>

Rambam Health Care Campus is a tertiary referral center that provides dermatology services to the entire northwest region of Israel, and is the only hospital in the region that offers immunopathology services for skin diseases. Therefore, patients with suspected pemphigus in the region are referred to this center. In order to examine whether there is an

ethnic predisposition for pemphigus, we assessed the incidence rate in 2 different ethnic populations in northern Israel (ie, Jews and Arabs). Although Judaism is a religion, it is also considered an ethnic group because the genetic background of Jews is quite distinct. In HLA studies, for example, Jews are regarded as a separate ethnicity, with additional subdivision into Ashkenazi and non-Ashkenazi groups.

Inclusion criteria were patients living in either Haifa or the northern districts who had newly diagnosed pemphigus. Pemphigus was diagnosed as a blistering disease of the skin or mucous membranes, in conjunction with characteristic histopathologic results showing intraepidermal blisters and acantholytic keratinocytes, and with positive results on  $\geq 1$  of the following tests: 1) intercellular deposits of IgG in the epidermis by direct immunofluorescence (DIF) studies; 2) intercellular circulating antibodies as shown using monkey esophagus and a standard indirect immunofluorescence (IIF) technique; 3) the presence of circulating IgG antibodies against Dsg3 or Dsg1 using an enzyme-linked immunosorbent assay<sup>12</sup>; or 4) circulating IgG antibodies against Dsg3 or Dsg1 using immunoblotting as described.<sup>13,14</sup>

According to our hospital's standard practice, all patients with newly diagnosed pemphigus are admitted to the inpatient ward of the Department of Dermatology and undergo a thorough medical history.

### Statistical analysis

Incidence rates were estimated as the ratios of the number of newly diagnosed cases of pemphigus for the years 2000 to 2015 over 16 times the 2008 census population obtained from the Israel Central Bureau of Statistics. Trends over time were tested by Poisson regression. For each incidence rate, an exact 95% confidence interval (CI) was obtained based on the Poisson distribution. Incidence rates were estimated

## CAPSULE SUMMARY

- A high incidence of pemphigus has been observed in Ashkenazi Jews and individuals of Mediterranean ancestry.
- Striking differences were found in the incidence rate and age of onset of pemphigus in 2 ethnic populations (Jews and Arabs) in one confined geographic area in northern Israel.
- The findings support a role for genetics in the etiology of pemphigus.

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