Prevalence and Age Distribution of Pemphigus and Pemphigoid Diseases in Germany


TO THE EDITOR

Autoimmune bullous diseases (AIBDs) are characterized by autoantibodies against structural proteins of the epidermis (pemphigus vulgaris and foliaceus) and dermal-epidermal junction (bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, and epidermolysis bullosa acquisita) (Schmidt and Groves, 2016). Clinically, blisters and erosions arise on skin and surface-close mucous membranes. Several reports have estimated the incidence of all AIBDs at between 13.3 and 66 cases per million people per year in Germany, the UK, Switzerland, France, Finland, Italy, and the US, with the highest incidences of bullous pemphigoid occurring in the population older than 80 years of age (150–300 cases/million people/year) and the lowest for epidermolysis bullosa acquisita (0.2–0.5 cases/million people/year) (Bertram et al., 2009; Brick et al., 2014; Cozzani et al., 2001; Forsti et al., 2014; Joly et al., 2012; Langan et al., 2008; Marazza et al., 2009; reviewed in Schmidt et al., 2015). In contrast, data about the prevalence of AIBDs are scarce.

We analyzed the database of a major German health insurance company, the Techniker Krankenkasse, which insures about 9.5 million individuals, representing about 12% of the German population. Diagnoses were based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification (ICD, www.icd-code.de) (2011) classification and included all living individuals in 2014. To control for a slightly different demographic composition of the insured individuals regarding age and sex, data were adjusted to the general German population based on data from the Federal Statistical Office of Germany for the year 2014 (www.destatis.de). We previously applied a similar approach to estimate the association of AIBDs with malignancies (Schulze et al., 2015).

The prevalence of pemphigus and pemphigoid diseases (excluding ICD L13.8, “other bullous dermatoses,” and L13.9, “bullous dermatosis, not further specified”) (ICD, 2011) in 2014 was calculated to 0.05%, resulting in a total number of about 40,400 patients in the total population of 80.925 million inhabitants in Germany. Bullous pemphigoid had the highest prevalence of all AIBDs (259.3 patients/million inhabitants), followed by pemphigus vulgaris (94.8 patients/million inhabitants), mucous membrane pemphigoid (24.6 patients/million inhabitants), and chronic bullous dermatosis of childhood (24.3 patients/million inhabitants < 18 years of age). Lower prevalences were seen for pemphigoid gestationsis (13.6/million females), pemphigus foliaceus (10.0/million) and epidermolysis bullosa acquisita (2.8/million) (Table 1). The prevalences for all analyzed ICD codes are shown in the Table 1.

Patients with more than one specific ICD code for AIBDs were allocated to the individual ICD codes according to their relative frequency. When a patient with more than one ICD code had the unspecified ICD code L10.9 (“pemphigus, not further specified”) or L12.9 (“pemphigoid, not further specified”) (ICD 2011) within the group of AIBD diagnoses, the patient was classified according to the specific code. Although the exact diagnosis could not be determined in these patients, the total prevalence of AIBDs was not affected.

In a previous study from Denmark in 2006 about the prevalence of autoimmune diseases, pemphigus (L10) and pemphigoid diseases (L12) were also included, and their prevalences were estimated to be 60 and 120 cases per million people, respectively (Eaton et al., 2010). The higher prevalence of pemphigoid diseases in the present study (data from 2014) may be explained in part by the improved diagnostic techniques and the increased incidence of bullous pemphigoid, for which the most common AIBD, for which a 2- to 4-fold increased incidence within the last decade has been reported in central Europe and the UK (Bertram et al., 2009; Joly et al., 2012; Langan et al., 2008). The higher prevalence of pemphigus diseases in Germany compared with Denmark may be, at least in part, due to the higher number of German inhabitants from the Mediterranean region, where the incidence of pemphigus is at least 2-fold higher (Hahn-Ristic et al., 2002).

Although the incidence of bullous pemphigoid has been reported to be about 10–15 times higher compared with pemphigus vulgaris/foliaceus (Bertram et al., 2009; Joly et al., 2012; Langan et al., 2008; Marazza et al., 2009), in this study, the prevalence of bullous pemphigoid was determined to be only 2.5-fold higher compared with that of pemphigus. This difference may reflect the much longer disease course in pemphigus patients well known to clinicians and the older age of patients with bullous pemphigoid. Moreover, the high 1-year mortality rate after diagnosis of bullous pemphigoid of between 20% and 40% (Cortes et al., 2011; Joly et al., 2012; Langan et al., 2008; Marazza et al., 2009; Parker et al., 2008; Rzany et al., 2002; reviewed in Schmidt et al., 2015) may also contribute to the observed difference in

Abbreviations: AIBD, autoimmune bullous disease; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification

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the incidence-to-prevalence ratios of bullous pemphigoid and pemphigus.

The prevalence of bullous pemphigoid of 259 cases per million people in this study indicates a disease duration of about 15 years based on the published incidence data of 13.4 cases per million people per year in a study from 2001–2002 in a single tertiary referral center in Lower Franconia, Germany (Bertram et al., 2009). A 2- to 4-fold increased incidence within one decade, as described from Lower Franconia, France, and the UK (Bertram et al., 2009; Joly et al., 2012; Langan et al., 2008) may result in an incidence of 30–40 cases per million people per year in 2014. Based on these data, a disease duration of 6–8 years can be calculated for bullous pemphigoid.

For analysis of the age distribution of major AIBDs, only patients with a distinct ICD coding were included. In line with previous reports, bullous pemphigoid and mucous membrane pemphigoid were more frequent in the elderly population, whereas pemphigus diseases predominately occurred in middle age (Schmidt et al., 2015).

Although it is known that most cases of epidermolysis bullosa acquisita affect the elderly, we saw a second peak of disease onset in the first three decades of life (Figure 1).

A limitation of this study was its dependence of ICD-10 coding of medical personnel of all specialties during both in- and outpatient treatments, as discussed previously (Hsu et al., 2016; Schulze et al., 2015). Coding errors may be caused by coding personnel who are not familiar with the sophisticated nomenclature of AIBDs or who do not appreciate the subtle differences between the different codes and the AIBDs. This assumption is supported by the relatively high number of unspecific coding (L10.9 and L12.9), which accounted for 15% of AIBD diagnoses.

An estimation of the coding quality may be derived from pemphigoid gestations, an AIBD occurring during pregnancies or the postpartum period (Schmidt and Zillikens, 2013). Pemphigoid gestations was diagnosed in no men but in 23 women older than 50 years, resulting in a false-coding rate of 4.5%. To further evaluate the data quality, three other chronic inflammatory dermatoses with known prevalences in Germany were included and were in line with previously reported prevalence data (psoriasis, 2.5%; alopecia areata, 0.2%; vitiligo, 0.5%) (Augustin et al., 2010; Gilhar et al., 2012; Taieb and Picardo, 2009) (Table 1). The lower prevalence of psoriasis in this study may be explained by the restriction to L40.0 (psoriasis vulgaris), in contrast to the study by Augustin et al. (2010) that evaluated all psoriasis ICDs including L40.9 (“psoriasis, not further specified”). Another shortcoming of this approach is that some relevant AIBDs, such as linear IgA disease in adults and anti-p200/laminin-γ1 pemphigoid could not be analyzed because of the lack of specific ICD-10 codes. Latter two diseases are coded as L12.8 (other pemphigoid disorders).

When analyzing the age distribution of L12.2, “chronic bullous dermatosis of childhood,” most patients (63%) were older than 18 years, with a median age of 47 years. The most likely explanation for this systematic miscoding is the
synonymous use of chronic bullous dermatosis of childhood and linear IgA dermatosis of childhood. This may have led many clinicians to code adult patients with linear IgA diseases as L12.2 (instead of L12.8). This mistake may have also been fostered by the lack of a specific ICD code for linear IgA disease of adults (see above). We, therefore, speculate that most adult patients encoded with L12.2 had linear IgA disease.

In summary, this study provides prevalences and age distributions of pemphigus and pemphigoid diseases based on a large patient collective in Germany.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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IL-17 Responses Are the Dominant Inflammatory Signal Linking Inverse, Erythrodermic, and Chronic Plaque Psoriasis


TO THE EDITOR

Inverse and erythrodermic psoriasis are rare subtypes of psoriasis. Whereas the former is characterized by shiny erythematous nonscaly plaques in the body folds, the latter has widespread redness with fine scale, covering over 80% of the body surface area, and can be life threatening. Both are clinical subtypes of chronic plaque psoriasis and often coexist or evolve from plaque psoriasis (Boyd and Menter, 1989; Omland and Gniadecki, 2015), but the pathogenic mechanisms involved are unknown, and current treatments are frequently unsatisfactory (Rosenbach et al., 2010).

To assess the shared and unique processes between chronic plaque, inverse, and erythrodermic psoriasis, we analyzed archived formalin-fixed paraffin-embedded biopsy samples of clinically and histologically confirmed chronic plaque (n = 12), inverse (n = 40), and erythrodermic psoriasis cases (n = 30) and healthy control skin (n = 12) using Affymetrix ST 2.1 arrays (Affymetrix, Santa Clara, CA). Compared with healthy skin, psoriatic plaque lesions yielded 2,450 differentially expressed genes (DEGs) (false discovery rate, FDR, P < 0.05), inverse psoriasis lesions yielded 408 DEGs (FDR, P < 0.05), and erythrodermic psoriasis lesions yielded 447 DEGs (FDR, P < 0.05) (Figure 1a). In total, 294 genes were found to be shared among the three disease subtypes (FDR, P < 0.05). Although the overlap accounted for only 12% of the DEGs in chronic plaque psoriasis, it accounted for 66% and 72% of DEGs in erythrodermic and inverse psoriasis, respectively.

Disease processes specific to each psoriasis subtype were analyzed using Ingenuity Pathway Analysis (Qiagen, Redwood City, CA). Canonical processes unique to chronic plaque psoriasis included protein ubiquitination pathway (P = 2.10 × 10−22), oxidative phosphorylation (P = 3.81 × 10−13), glucocorticoid receptor signaling (P = 2.44 × 10−12), mitochondrial dysfunction (2.26 × 10−10), and mTOR signaling (P = 4.13 × 10−07). Genes unique to chronic plaque psoriasis included NFKBIZ (3.6-fold increase) and DDX58 (2.4-fold increase), genes recently implicated in the pathogenesis of psoriasis (Johansen et al., 2015; Tsoi et al., 2015). Overlapping canonical processes between plaque and inverse psoriasis included epithelial adherens junction signaling (P = 2.52 × 10−4) and unfolded protein responses (P = 1.19 × 10−4), whereas the overlap between plaque and erythrodermic psoriasis included remodeling of epithelial adherence junction (P = 6.8 × 10−04) and phagosome maturation (P = 7.0 × 10−04). The numbers of genes unique to inverse and erythrodermic psoriasis were too small for analyses of enriched biologic processes (see Supplementary Materials online). Genes shared among all three clinical presentations included S100A7 (32-fold increase in plaque psoriasis), 8.7-fold increase in inverse psoriasis, and 6-fold increase in erythrodermic psoriasis, KRT16 (15-, 5-, and 4.8-fold increases, respectively), IL36G (10-, 3.7- and 3.9-fold increases, respectively), and human β-defensin 2 (hBD2/DEFB4) (10-, 4.5-, 3.5-fold increases, respectively). These were confirmed by immunohistochemistry (Figure 1b).

The most enriched canonical pathway from the group of genes shared among plaque, inverse, and erythrodermic psoriasis included IL-17a signaling (P = 3.24 × 10−09), followed by p38 mitogen-activated protein kinase signaling (P = 5.8 × 10−05) and communication between innate and adaptive immune cells (P = 5.35 × 10−04). The key biologic nodes in the shared gene set included keratinocyte differentiation, regulation of endopeptidase activity, response to external biotic stimulus, viral genome replication, and response to cytokines (Figure 2a).

Next screened the overlapping gene set to determine if such genes were disproportionately induced by cytokine treatments applied to cultured keratinocytes using cytokine-response analyses previously described by our group (Swindell et al., 2013a; Swindell et al., 2013b). Consistent with the Ingenuity pathway analysis results, the overlapping gene set among the three transcriptomes was most strongly enriched with respect to genes induced by IL-17a in cultured keratinocytes, with strong enrichment also observed with respect

Abbreviations: DEG, differentially expressed gene; FDR, false discovery rate

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