

Dermatitis Herpetiformis and Celiac Disease Increase the Risk of Bullous Pemphigoid



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Bullous pemphigoid (BP) and dermatitis herpetiformis (DH) are autoimmune bullous skin diseases. DH has been described to evolve into BP and the two diseases can have overlapping clinical appearances and diagnostic findings, but the association between DH and BP has not previously been studied in a large population. To evaluate DH and celiac disease as risk factors for BP, we conducted a retrospective case-control study of patients with BP and matched controls with basal cell carcinoma diagnosed in Finland between 1997 and 2013. A total of 3,397 patients with BP and 12,941 controls were included in the study. Forty-one (1.2%) BP patients and 7 (0.1%) controls had preceding DH. Diagnosed DH increased the risk of BP 22-fold (odds ratio = 22.30; 95% confidence interval = 9.99–49.70) and celiac disease 2-fold (odds ratio = 2.54; 95% confidence interval = 1.64–3.92) compared to controls. Eighteen (43.9%) of the patients who had DH and subsequent BP had bought dapsone during the 2 years prior to their BP diagnosis. Mean time between diagnosed DH and BP was 3 years. We conclude that diagnosis of DH is associated with a striking increase in the risk for BP.

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INTRODUCTION

Bullous pemphigoid (BP) and dermatitis herpetiformis (DH) are subepidermal blistering skin diseases of autoimmune origin. Pruritus is intense in both diseases, but in BP, tense bullae are also typically present, while in DH excoriations and erosions secondary to scratching are mainly seen (Bağc et al., 2017; Bolotin and Petronic-Rosic, 2011a). BP is relatively rare, with incidence varying from 2.5 to 43 individuals per million, and it mostly affects older people, typically first appearing at around 80 years of age (Baican et al., 2010; Brick et al., 2014; Försti et al., 2014; Joly et al., 2012; Langan et al., 2008; Marazza et al., 2009). By contrast, DH is generally a disease of younger people; a Finnish cohort study reported a mean age of 43 years at diagnosis (Salmi et al., 2011), but in a study of 264 DH patients from the United States, the mean age at diagnosis was 49 years (Alonso-Llamazares et al., 2007). In the last few decades, studies from different parts of the world have estimated the incidence of DH to be between 11.2 and 75.3 per 100,000 (Collin et al., 2017; Salmi et al., 2011; West et al., 2014). Interestingly, the incidence of DH has decreased over time (Salmi et al., 2011) while the incidence of BP is increasing (Langan et al., 2008; Joly et al., 2012; Försti et al., 2014).

Autoantibodies against collagen XVII (BP180) in the cutaneous basement membrane zone are central in the pathogenesis of BP, however, the factors leading to autoantibody production and disease onset still need to be elucidated (Bağc et al., 2017; Schmidt and Zillikens, 2013). DH is considered to be a cutaneous form of celiac disease (CD), in which ingestion of gluten leads to the production of autoantibodies against the epidermal enzyme transglutaminase-3 (Collin et al., 2017). Direct immunofluorescence microscopy (DIF) is used as a diagnostic tool in both diseases: in BP, DIF reveals linear deposits of IgG and/or complement C3 in the dermo-epidermal junction (Bağc et al., 2017), whereas in DH, DIF shows granular IgA deposits in the papillary dermis (Reunala et al., 2015). In both BD and DH, a diagnosis is based on the combination of DIF findings, clinical appearance, and histopathologic and serologic measures, including BP180-NC16A ELISA and indirect immunofluorescence assay on salt split skin (Baum et al., 2014). In BP, typical clinical findings are pruritus and bullae. Eczematous and/or urticarial lesions may also be seen and sometimes these are the only manifestation of the disease (Bağc et al., 2017; Schmidt and Zillikens, 2013). The clinical appearance of DH often includes pruritic papules and vesicles, but sometimes consists of only symmetrical patterns of excoriations on the extensor surfaces of the extremities, buttocks, scalp, knees, and elbows, due to scratching (Bolotin and Petronic-Rosic, 2011a; Collin et al., 2017).

Treatment of BP tends to include oral and topical corticosteroids, and other immunosuppressive agents (e.g., methotrexate, dapsone, azathioprine, and mycophenolate mofetil) and doxycycline are often used, either as adjuvant therapy alongside corticosteroids or alone as monotherapy (Bağc et al., 2017; Schmidt and Zillikens, 2013). The management of DH is centered upon a lifelong gluten-free diet. However, due to its rapid effect on pruritus, dapsone is frequently used in the initiation of therapy and in patients

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Abbreviations: BP, bullous pemphigoid; BCC, basal cell carcinoma; CD, celiac disease; DH, dermatitis herpetiformis; DIF, direct immunofluorescence analysis; ICD, International Classification of Diseases

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whose symptoms persist despite the gluten-free diet (Bolotin and Petronic-Rosic, 2011b; Reunala et al., 2015; Collin et al., 2017).

Neurologic conditions are well known to be associated with BP, and psychiatric diseases, psoriasis, hypertension, hematologic malignancies, and diabetes have also been reported as comorbidities of BP (Atzmony et al., 2017; Chen et al., 2011; Kibsgaard et al., 2017; Kridin and Bergman, 2017; Schulze et al., 2015; Sim et al., 2017). DH is associated with type I diabetes, thyroid diseases, and other autoimmune diseases (Bolotin and Petronic-Rosic, 2011a; Collin et al., 2017). Furthermore, patients with DH who do not adhere to a gluten-free diet appear to carry an elevated risk of developing lymphomas (Hervonen et al., 2005; Lewis et al., 1996).

Case reports of DH evolving into BP have been published (Ameen et al., 2000; Didona and Di Zenzo, 2018; Honeyman et al., 1972; Murphy et al., 2003), but larger studies of this probable association are currently lacking. The aim of the present study was to evaluate DH as a risk factor for BP in the setting of a Finnish nationwide registry-based case-control study.

RESULTS

Characteristics of patients and controls

The database search from the Finnish Care Register for Health Care returned data for 4,524 patients who received a diagnosis of BP between 1987 and 2013. The present analysis employed data from a subgroup of 3,397 of these patients who were diagnosed with BP between the years 1997 and 2013. A total of 66,138 basal cell carcinoma (BCC) patients were identified and 12,941 of these were selected randomly to be matched to the BP population by age, sex, and year of diagnosis in a 4:1 ratio. Due to the incomplete availability of drug reimbursement data for some of the BCC controls, 579 of the BP patients had fewer than the intended four matched controls. The characteristics of the BP and control groups are shown in Table 1.

Risk for BP after diagnosis of DH or CD, time intervals between diagnoses and medication use

We identified 41 (1.2%) individuals in the BP group with preceding DH, whereas in the BCC group there were only 7 (0.1%). Preceding CD was found in 34 (1.0%) BP patients and 53 (0.4%) in the control group. In our study population, 12 (29%) of the BP patients with DH also had CD.

Patients with CD had a twofold greater risk for BP than those without. Remarkably, patients with DH had a 22-fold elevated risk for BP (Table 2). Differences between sexes were not statistically significant, although there was a trend toward a greater risk for BP after DH in males than in females (Table 3).

Mean age at the time of the BP diagnosis was 68.8 (range 44–89) years in those with preceding DH, and 76.7 (range 40–102) years in the group of BP patients with no preceding DH. Mean age at the time of diagnosis of DH was 64.9 years (median 64.0 years, first quartile 54.0 years, third quartile 78.0 years) in the BP group and 65.6 years (median 73.0 years, first quartile 56.0, years third quartile 76.5 years) in the BCC group. The mean time intervals between the diagnosis of DH and that of BP or BCC were 3.3 years and 10.0 years,

Table 1. Subject characteristics at the time of the diagnosis of bullous pemphigoid or basal cell carcinoma

Characteristics	Cases (n = 3,397)	Controls (n = 12,941) ¹
Female, n (%)	2,028 (59.7)	7,766 (60.0)
Male, n (%)	1,369 (40.3)	5,175 (40.0)
Age, years, mean (range)	76.6 (40–102)	76.7 (40–101)
Neurologic or psychiatric disease, ² n (%)	1,612 (47.5)	4,367 (33.8)

¹Age, sex, and year of the diagnosis matched in 1:4 ratio. Due to availability of drug reimbursement data, 579 patients had fewer than four basocellular carcinoma controls.

²Alzheimer's disease, vascular dementia, other/unspecified dementia, Parkinson's disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, epilepsy, schizotypal and delusional disorder, schizophrenia, bipolar affective disorder, major depressive disorder, neurotic, stress-related and somatoform disorders, and personality disorders.

respectively, while the mean times between the diagnosis of CD and BP or BCC were 4.9 years and 7.2 years, respectively.

Using data on reimbursed drugs from the Social Insurance Institution of Finland, we identified all of the DH patients that had used dapsone. Eighteen of the patients with DH had used dapsone in the 2 years preceding the diagnosis of BP and, of those, 14 had received dapsone during the 6 months prior to the diagnosis.

Use of diabetes medication of the dipeptidyl peptidase-4 inhibitors class, particularly vildagliptin, has been described recently as a risk factor for BP (Benzaquen et al., 2018; Varpuluoma et al., 2018). To exclude the possibility that use of such medications could have confounded the association we found between DH and BP, we investigated the use of these drugs by examining the aforementioned data set regarding reimbursed drugs. None of the DH patients in either the BP or BCC group had received a dipeptidyl peptidase-4 inhibitor in the 2 years preceding their BP or BCC diagnosis, and only one patient in the BP group with preceding CD had used a dipeptidyl peptidase-4 inhibitor in the previous 2 years.

DISCUSSION

This study of Finnish BP patients reveals a strong association between DH and BP. Neither DH nor CD were analyzed in previous studies of BP comorbidities (Bastuji-Garin et al., 2011; Chen et al., 2011; Jedlickova et al., 2010; Jeon et al., 2018; Kibsgaard et al., 2017; Sim et al., 2017; Teixeira et al., 2014). In a British interview-based study of BP and other autoimmune disorders, neither DH nor CD were among the diseases about which the participants (n = 108) were asked (Taylor et al., 1993). Dermatitis herpetiformis and BP are both relatively rare diseases, so a large study population is required to discover any association between the two. Moreover, both DH and CD are more common in Finland than almost anywhere else in the world (Salmi et al., 2011), which may have allowed the present study's discovery of these associations. Additional studies of the risk for developing BP in a cohort of DH patients would help us to further confirm this association.

Table 2. Odds ratios for the development of bullous pemphigoid following a diagnosis of dermatitis herpetiformis or celiac disease

Preceding Disease	Group	Total, n	n (%)	OR (95% CI)
Dermatitis herpetiformis	BP	3,397	41 (1.2)	22.30 (9.99–49.70)
	BCC	12,941	7 (0.1)	ref
Celiac disease	BP	3,397	34 (1.0)	2.54 (1.64–3.92)
	BCC	12,941	53 (0.4)	ref

Abbreviations: BCC, basal cell carcinoma; BP, bullous pemphigoid; CI, confidence interval; OR, odds ratio; ref, reference.

The clinical appearance and DIF findings of DH are usually easily distinguishable from those of BP, but case reports with overlapping clinical presentation and immunofluorescence microscopy findings have been described (Honeyman et al., 1972; Jablonska et al., 1976; Sander et al., 1989; Schulze et al., 2013; Setterfield et al., 1997; Vaira et al., 2013). For example, Ameen et al. (2000) described a patient who had pruritic papulovesicular eruptions and whose DIF findings showed deposition of IgA and C3 within the papillary dermis. The patient responded well to a gluten-free diet and dapsone treatment, but 11 years later developed an apparently different blistering eruption, and DIF showed IgG and C3 in the basement membrane zone as well as fibrillar IgA staining in the dermal papillae (Ameen et al., 2000). Epitope spreading was suggested as an explanation for the disease evolution seen in this case. Epitope spreading is a phenomenon in which an immune response is developed to one or more other epitopes in addition to the dominant epitope. It is known to exist in autoimmune bullous diseases, including BP (Chan et al., 1998; Didona and Di Zenzo, 2018). Epitope spreading has been reported to occur often during the first 3 months after a diagnosis of BP and is associated with disease severity (Di Zenzo et al., 2011). Epitope spreading has also been hypothesized to explain the onset of DH in patients with CD (Kárpáti et al., 2018). With regard to the present study, epitope spreading is a possible immunomechanism driving the association between DH and BP, but unfortunately, because this was a registry-based study, we had no access to the DIF findings or serum samples of the DH patients who developed BP subsequently and, therefore, we were unable to confirm or disprove this hypothesis.

Several physical factors have been reported to trigger BP. Exposure to UV rays or other forms of radiation, surgical wounds and ostomies, photodynamic therapy, burns, and several different types of mechanical trauma, have all been reported to have triggered BP (Dănescu et al., 2016; Mai et al., 2018; Rakvit et al., 2011). Physical factors causing tissue damage may disturb the basement membrane zone or activate the inflammatory processes and thus contribute to BP onset in susceptible individuals. Our finding that DH was associated with distinctly higher risk for BP than was CD leads us to hypothesize that active cutaneous inflammation and scratching in DH could act as triggering factors for BP. In a Finnish study of 311 DH patients, only 8% needed dapsone to control their skin symptoms (Hervonen et al., 2012). In the present study 34% (14 of 41) of the patients with DH and subsequent BP had used dapsone during the 6 months

Table 3. Odds ratios for the development of bullous pemphigoid following a diagnosis of dermatitis herpetiformis or celiac disease by sex

Preceding Disease/Sex	Group	Total, n	n (%)	OR (95% CI)
Dermatitis herpetiformis/men	BP	1,369	20 (1.5)	73.30 (9.82–546)
	BCC	5,175	1 (0.0)	ref
Dermatitis herpetiformis/women	BP	2,028	21 (1.0)	13.70 (5.54–34.00)
	BCC	7,766	6 (0.1)	ref
Celiac disease/men	BP	1,369	12 (0.9)	2.61 (1.24–5.49)
	BCC	5,175	18 (0.3)	ref
Celiac disease/women	BP	2,028	22 (1.1)	2.50 (1.46–4.28)
	BCC	7,766	35 (0.5)	ref

Abbreviations: BCC, basal cell carcinoma; BP, bullous pemphigoid; CI, confidence interval; OR, odds ratio; ref, reference.

preceding their BP diagnosis. This most likely reflects the activity of the DH skin symptoms and itching, which may in turn contribute to the onset of BP.

Genetic predisposition for both BP and DH has been linked to certain HLA alleles. HLA-DQB1*0301 is overrepresented among BP patients of various ethnic origins (Amber et al., 2017; Sun et al., 2018). Susceptibility for DH and CD is known to be associated with the HLA-DQ2 and DQ8 haplotypes (Collin et al., 2017; Kaukinen et al., 2002; Spurkland et al., 1997). Vaira et al. (2013) described a patient with BP who later developed concomitant DH; this patient had an HLA profile that predisposed them to both BP and DH. However, any significance of HLA types in the association between DH and BP is currently unknown because, to the best of our knowledge, HLA genetics in patients with concomitant DH and BP have not yet been studied.

In the present study, the mean time from the diagnosis of DH to the diagnosis of BP was 3 years and the mean time between CD and BP diagnosis was 4.9 years. In case reports, DH has preceded BP by between 4 months and 25 years (Ameen et al., 2000; Murphy et al., 2003; Setterfield et al., 1997). Reports of the intervals between the onset of comorbid diseases and subsequent diagnosis of BP vary widely: In our recent study of neurologic and psychiatric comorbidities, a BP diagnosis was preceded by a diagnosis of dementia, multiple sclerosis, or psychiatric diseases by a mean interval of 3, 12, and 7–11 years, respectively (Försti et al., 2016). In a Korean cohort of 3,485 BP patients, dementia, Parkinson's disease, and epilepsy preceded BP by 3, 4, and 2 years, respectively, and comorbid rheumatoid arthritis occurred 5 years before BP (Chen et al., 2011). In the Korean study the mean time between psoriasis and BP diagnoses was 3 years (Chen et al., 2011), but a recent study from Israel reported a very long mean interval of 25 years between diagnoses of psoriasis and BP (Kridin and Bergman, 2017). It is worth noting that, in the present study, mean age at time of DH diagnosis was 64.9 years in patients who later developed BP, whereas the mean age at DH diagnosis was 49 years in Finland during years 2000–2009 (Salmi et al., 2011). This suggests that physicians should be wary of the possible development of BP when treating patients with late-onset DH who develop itch or other novel skin symptoms.

A major strength of our study is that it utilized one of the largest nationwide BP cohorts ever studied (Försti et al., 2017) and this cohort was formed using data from the Finnish Care Register for Health Care, which is known to be an accurate database (Sund, 2012). We also had access to data on all reimbursed drugs received by the patients.

The limitations in the present study arise from the registry-based study setting. Because the data we used were routinely gathered by the registry, we cannot be certain that all of the reported BP and DH cases were confirmed immunologically. Furthermore, we did not have access to information regarding the actual onset of the diseases, results from the diagnostic tests, or patients' samples. Therefore, we could not completely rule out the existence of other variants of pemphigoid, such as epidermolysis bullosa acquisita, p200 pemphigoid, and laminin-332 pemphigoid among BP patients. However, in Finland, immunofluorescence microscopy tests are performed in the hospital setting and diagnoses of DH and BP are generally made in hospital dermatology clinics, so the recorded diagnoses can be considered reliable.

In summary, we report a significant association between DH and BP. In daily practice, it is important for the dermatologist to recognize the risk of DH evolving to BP if the clinical picture of a patient's disease changes or they become unresponsive to the gluten-free diet. Advancing our knowledge of the comorbidities of BP may help us to understand the process that leads to the breaking of cutaneous immunotolerance in BP.

METHODS

Populations and databases

This was a retrospective database study of patients diagnosed with BP in Finland between January 1, 1997 and December 31, 2013. Patient records were obtained from the Finnish Care Register for Health Care, which contains data on the diagnosis codes of hospitalized inpatients from the year 1994 onwards and of outpatient visits from 1998 onward, but no detailed clinical information. The Finnish Care Register for Health Care contains data collected from all hospitals in Finland that are maintained by local authorities, municipal federations, and central government, and from the largest of the country's private hospitals. As described previously (Försti et al., 2016), patients in the BP group were selected by their BP diagnoses, defined by the International Classification of Diseases (ICD)-9 codes 6945A and 6945B, and ICD-10 code L12.0. The control population consisted of patients diagnosed with BCC as defined by the ICD-9 codes 1730A–1739A and ICD-10 codes C44.01, C44.11, C44.21, C44.31, C44.41, C44.51, C44.61, C44.71, C44.81, and C44.91 over the same time period described. BCC was selected because, like BP, it affects elderly people but is not an inflammatory skin disease (Diepgen and Mahler, 2002; Wong et al., 2003). The BCC control patients were matched by sex, age, and year of the diagnosis (within 2 years). From the same registry, we also collected data regarding all other diagnoses received by our selected populations. Patients aged younger than 40 years were excluded from the study because BP is extremely rare in younger age groups. Diagnoses of DH and CD in the study populations were identified by searching the same database for ICD-9 and ICD-10 codes 6940A and L13.0 for DH and 5790A and K90.0 for CD.

Data on drugs received by patients and controls were obtained from the Social Insurance Institution of Finland. This registry

includes reliable data on all reimbursed drugs from the year 1995 onwards. In order to obtain complete medication data for the 2 years preceding the first BP diagnosis, only patients diagnosed between the years 1997 and 2013 were included in the present study. The unique personal identification number given to every resident of Finland was used to combine the data from different databases. Data were collected using ATC-code J04BA02 for dapsone, A10BH01–A10BH51 for dipeptidyl peptidase-4 inhibitors, and A10BD07–A10BD13 for combinations of dipeptidyl peptidase-4 inhibitor and other diabetes medications.

Statistical analyses

The characteristics of the study population are presented as proportions and means. The associations of BP with DH and CD were evaluated using a conditional logistic regression model. Odds ratios and 95% confidence intervals are presented. Because previous analyses of the same study population showed that psychiatric and neurologic diseases are associated with BP (Försti et al., 2016), the following variables were considered as potential confounding factors: Alzheimer's disease, vascular dementia, other/unspecified dementia, Parkinson's disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, epilepsy, schizotypal and delusional disorder, schizophrenia, bipolar affective disorder, major depressive disorder, neurotic, stress-related and somatoform disorders, and personality disorders. Because those had no effect on the main outcome, only unadjusted results are shown. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Cary NC). Two-sided *P* values <0.05 were considered statistically significant.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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