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Dermatitis herpetiformis and celiac disease increase the risk of bullous pemphigoid

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Short Title: Dermatitis herpetiformis increases the risk of bullous pemphigoid

Abbreviations: BP, bullous pemphigoid; BCC, basal cell carcinoma; CD, celiac disease; CRCH, Finnish Care Register for Health Care; DIF, direct immunofluorescence analysis; DH, dermatitis herpetiformis; DPP-4i, dipeptidyl peptidase-4 inhibitor.

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Abstract

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 (CD) 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 3397 patients with BP and 12941 controls were included in the study. Forty-one (1.2%) of BP patients and seven (0.1%) of controls had preceding DH. Diagnosed DH increased the risk of BP 22-fold (Odds Ratio [OR] 22.30, 95% confidence interval [CI] 9.99 - 49.70) and CD two-fold (OR 2.54, 95% CI 1.64 - 3.92) compared to controls. Eighteen (43.9%) of the patients who had DH and subsequent BP had bought dapsone during the two years prior to their BP diagnosis. Mean time between the diagnosed DH and BP was 3 years. We conclude that diagnosis of DH is associated with a striking increase in the risk for BP.

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 (Bolotin and Petronic-Rosic, 2011a; Bağcı et al, 2017). 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 (Marazza et al, 2009; Baican et al, 2010; Langan et al, 2008; Joly et al, 2012; Försti et al, 2014; Brick et al, 2014). By contrast, DH is generally a disease of younger people: a Finnish cohort study reported a mean age of 43 at diagnosis (Salmi et al, 2011), but in a study of 264 DH-patients from USA the mean age at the diagnosis was 49 years (Alonso-Llamazares et al, 2007). In the last few decades, studies from different parts of world have estimated the incidence of DH to be between 11.2 and 75.3 per 100 000 (Salmi et al, 2011; West et al, 2014; Collin et al, 2017). 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 (Schmidt and Zillikens, 2013; Bağcı et al, 2017). 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 (TG3) (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 (Bağcı 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 histopathological and serological 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 (Schmidt and Zillikens, 2013; Bağcı et al, 2017). 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, mycophenolate mofetil) and doxycycline are often used, either as adjuvant therapy alongside corticosteroids or alone as monotherapy (Schmidt and Zillikens, 2013; Bağcı et al, 2017). 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 whose symptoms persist despite the gluten-free diet (Bolotin and Petronic-Rosic, 2011b; Reunala et al, 2015; Collin et al, 2017).

Neurological conditions are well known to be associated with BP, and psychiatric diseases, psoriasis, hypertension, hematological malignancies and diabetes have also been reported as comorbidities of BP (Chen et al, 2011; Schulze et al, 2015; Atzmony et al, 2017; Kibsgaard et al, 2017; Sim et al, 2017; Kridin and Bergman, 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 (Lewis et al, 1996; Hervonen et al, 2005).

Case reports of DH evolving into BP have been published (Honeyman et al, 1972; Ameen, Bhogal and Black, 2000; Murphy et al, 2003; Didona and Di Zenzo, 2018), 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 (CRHC) returned data for 4524 patients who received a diagnosis of BP between 1987 and 2013. The present analysis employed data from a subgroup of 3397 of these cases, who were diagnosed with BP between the years 1997 and 2013. A total of 66138 basal cell carcinoma (BCC) cases were identified and 12941 of these were randomly selected 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 individuals (1.2%) in the BP group with preceding DH, whereas in the BCC group there were only seven (0.1%). Preceding CD was found in 34 BP patients (1.0%) and 53 of the control group (0.4%). In our study population, 12 (29%) of the BP patients with DH also had CD.

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

The mean age at the time of the BP diagnosis was 68.8 years (range 44 – 89 years) in those with preceding DH and 76.7 years (range 40 – 102 years) in the group of BP patients with no preceding DH. The mean age at the time of diagnosis of DH was 64.9 years (median 64.0, first quartile: 54.0, third quartile 78.0) in the BP group and 65.6 (median 73.0, first quartile: 56.0, third quartile: 76.5) in the BCC group. The mean time intervals between the diagnosis of DH and that of BP or BCC were 3.3 and 10.0 years, respectively, while the mean times between the diagnosis of CD and that of BP or BCC were 4.9 and 7.2 years, respectively.

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

Use of diabetes medication of the dipeptidyl peptidase-4 inhibitors (DPP-4i) class, particularly vildagliptin, has recently been described 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 DPP-4i in the two years preceding their BP or BCC diagnosis, and only one patient in the BP group with preceding CD had used a DPP-4i inhibitor in the previous two years.

DISCUSSION

This study of Finnish BP patients reveals a strong association between DH and BP. Neither DH or CD were analyzed in previous studies of BP comorbidities (Jedlickova et al, 2010; Bastuji-Garin et al, 2011; Chen et al, 2011; Teixeira et al, 2014; Kibsgaard et al, 2017; Sim et al, 2017; Jeon et al, 2018). In a British interview-based study of BP and other autoimmune disorders, neither DH nor CD was 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.

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, Utz and Peters, 1989; Setterfield et al, 1997; Vaira et al, 2013; Schulze, 2013). For example, Ameen and coworkers described a patient who had pruritic papulovesicular eruptions and whose DIF findings showed deposition of IgA and C3 within the papillary dermis (Ameen et al, 2000). 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 three first 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, 2017). With regard to the present study, epitope spreading is a possible immunomechanism driving the association between DH and BP, but unfortunately, this being a registry-based study, we had no access to the DIF findings or serum samples of the DH patients who subsequently developed BP, and therefore were unable to confirm or disprove this hypothesis.

Several physical factors have been reported to trigger BP. Exposure to ultraviolet 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

(Rakvit et al, 2011; Dănescu et al, 2016; Mai et al, 2018). 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% (14/41) of the patients with DH and subsequent BP had bought dapsone during the 6 months 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 human leukocyte antigen (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 (Spurkland et al, 1997; Kaukinen et al, 2002; Collin et al, 2017). Vaira and co-authors described a patient with BP who later developed concomitant DH; this patient had an HLA profile which predisposed them to both BP and DH (Vaira et al, 2013). However, any significance of HLA types in the association between DH and BP is currently unknown, since, to the best of our knowledge, HLA genetics in patients with concomitant DH and BP has not yet been studied.

In the present study, the mean time from the diagnosis of DH to the diagnosis of BP was three years and the mean time between CD and BP diagnosis, 4.9 years. In case reports, DH has preceded BP by between 4 months and 25 years (Setterfield et al, 1997; Ameen et al, 2000;

Murphy et al, 2003). Reports of the intervals between the onset of comorbid diseases and subsequent diagnosis of BP vary widely: In our recent study of neurological and psychiatric comorbidities, a BP diagnosis was preceded by a diagnosis of dementia, multiple sclerosis or psychiatric diseases by a mean interval of three, 12 and 11 years, respectively (Försti et al, 2016). In a Korean cohort of 3485 BP patients, dementia, Parkinson's disease and epilepsy preceded BP by three, four and two years, respectively, and comorbid rheumatoid arthritis occurred five years before BP (Chen et al, 2011). In the Korean study the mean time between psoriasis and BP diagnoses was three 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, the mean age at the 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 CRHC, 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. Since the data we used were routinely gathered by the registry, we cannot be certain that all the reported BP and DH cases were immunologically confirmed. 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 complete 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. Furthering our knowledge of the co-morbidities 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 1st January 1997 and 31st December 2013. Patient records were obtained from the CRHC, which contains data on the diagnosis codes of hospitalized inpatients from the year 1994 onwards and of outpatient visits from 1998 onwards, but no detailed clinical information. The CRCH 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 basal cell carcinoma (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 as that described above. 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 gender, age (within two years) and year of the diagnosis. From the same registry we also collected data regarding all other diagnoses received by our selected populations. Patients aged under 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 two 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 (DPP-4i) and A10BD07-A10BD13 for combinations of DPP-4i 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 (ORs) and 95% Confidence Intervals (CIs) are presented. Since previous analyses of the same study population showed that psychiatric and neurological diseases are associated with BP (Försti et al, 2016), 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. Since those had no effect on the main outcome, only unadjusted results are shown. All Statistical analyses were performed using the SAS software package (version 9.4; SAS Institute, Inc). Two-sided P-values less than 0.05 were considered statistically significant.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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

	Cases n = 3397 (%)	**Controls n = 12941 (%)[1]**
Female	2028 (59.7)	7766 (60.0)
Male	1369 (40.3)	5175 (40.0)
Mean age, years (range)	76.6 (40 – 102)	76.7 (40 – 101)
Neurological or psychiatric disease[2]	1612 (47.5)	4367 (33.8)

[1] Age, 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.

[2] 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.

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

Preceding disease	Group	total	N (%)	OR (CI)
Dermatitis herpetiformis	BP	3397	41 (1.2)	22.30 (9.99 - 49.70)
	BCC	12941	7 (0.1)	Reference
Celiac disease	BP	3397	34 (1.0)	2.54 (1.64 - 3.92)
	BCC	12941	53 (0.4)	Reference

BP: bullous pemphigoid; BCC: basal cell carcinoma; CI: confidence interval; OR: odds ratio

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

Preceding disease / gender	Group	total	N (%)	OR (95% CI)
Dermatitis herpetiformis/men	BP	1369	20 (1.5)	73.30 (9.82 – 546)
	BCC	5175	1 (0.0)	Reference
Dermatitis herpetiformis / women	BP	2028	21 (1.0)	13.70 (5.54 – 34.00)
	BCC	7766	6 (0.1)	Reference
Celiac disease / men	BP	1369	12 (0.9)	2.61 (1.24 – 5.49)
	BCC	5175	18 (0.3)	Reference
Celiac disease / women	BP	2028	22 (1.1)	2.50 (1.46 – 4.28)
	BCC	7766	35 (0.5)	Reference

BP: bullous pemphigoid; BCC: basal cell carcinoma; CI: confidence interval; OR: odds ratio