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Comorbid diseases among bullous pemphigoid patients in Germany: new insights from a case-control study

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Summary

Background and objectives: Bullous pemphigoid (BP) is associated with neuropsychiatric disorders. Other comorbid diseases are discussed controversially. We evaluated the prevalence of comorbidity in BP patients in a representative area of Germany.
Patients and methods: Medical files of all BP patients treated at the Department of Dermatology, University Hospital Würzburg, Germany, between June 2002 and May 2013 were retrospectively reviewed. Bullous pemphigoid was diagnosed based on established criteria. For each patient, two controls were individually matched. Records were evaluated for age, sex, laboratory values, concomitant medication and comorbidity. Conditional logistic regression, multivariable regression analysis and complex regression models were performed to compare results.
Results: 300 BP patients were identified and compared to 583 controls. Bullous pemphigoid was associated with neuropsychiatric disorders as well as laboratory abnormalities including leukocytosis and eosinophilia. Importantly, a highly significant association of BP with anemia (OR 2.127; 95 % CI 1.532–2.953) and renal impairment (OR 2.218; 95 % CI 1.643–2.993) was identified. No association was found with malignancy and arterial hypertension.
Conclusions: Our data revealed an increased frequency of anemia and renal impairment in BP patients. In accordance with previous studies the strong association for neuropsychiatric disorders was confirmed ($p < 0.0005$).

Introduction

Bullous pemphigoid (BP) is the most common blistering autoimmune disease in industrialized countries. It mostly affects elderly people, which is reflected by a rising incidence with increasing age [1]. The etiology of BP remains unclear and is currently under discussion. BP is characterized by circulating IgG autoantibodies against the hemidesmosomal proteins BP180 and/or BP230 and a subsequent cellular immune response [2]. Various case reports and, more recently, case-controlled studies provided evidence of associated comorbid diseases in BP patients. Initially, autoimmune diseases, particularly rheumatoid arthritis and malignancies, were in the focus of interest [3, 4]. The attention subsequently turned to diabetes mellitus [5]. In the last years, there has been growing evidence that BP is associated with neurologic and psychiatric disorders. Association with multiple sclerosis, dementia, Parkinson's disease, epilepsy and cerebrovascular disorders was documented and confirmed by several studies [6–12]. In addition, a variety of comorbid disorders including arterial hypertension have been described [13, 14]. The underlying pathophysiologic mechanisms resulting in these associations remain yet unclear. Nevertheless, knowledge of comorbid diseases is essential to optimize patient care especially with regard to additional diagnostic measures besides the conformation of the skin disease. The aim of this retrospective case-control study was to analyze associations and comorbidity in all patients with newly diagnosed BP at the Department of Dermatology at the University Hospital Würzburg between June 2002 and May 2013 and to compare the results with previous studies.

Materials and Methods

Patients

Medical records of 300 consecutive BP patients were available for retrospective evaluation. Individual patients were eligible for study inclusion if they were admitted between June 2002 and May 2013 to our department, a tertiary university hospital-based referral center, and had a definite diagnosis of BP (ICD-10 code L12.0). Diagnosis was verified by manual review of all medical records according to established criteria [15]: *(1)* typical clinical features, *(2)* positive direct immunofluorescence microscopy (DIF) of biopsies that were taken from perilesional skin (linear deposits of IgG and/or C3 at the dermoepidermal junction were considered as diagnostic) and/or *(3)* detection of anti-BP180 IgG antibodies in the patients' serum by ELISA (MESACUP BP180®, MBL, Nagoya, Japan). In cases where DIF was positive while anti-BP180 IgG antibodies could not be detected by ELISA in the corresponding sera, BP was diagnosed considering the results of indirect immunofluorescence on salt-split skin, immunoblotting and/or immunomapping.

All patient-related diagnostic and therapeutic procedures were part of routine practice. Written informed consent was obtained for biopsies.

Controls

For each BP patient, two controls were individually matched. Controls were selected from inpatients who had been referred for surgery of basal cell carcinoma. Patients with a history of basal cell nevus syndrome or bullous autoimmune diseases were not included. Matching considered three aspects: (1) sex, (2) age (± 4 years) and (3) year (± 4 years) the individual was admitted to the Department of Dermatology at the University Hospital Würzburg. According to these criteria, 583 controls were allocated. For three BP patients only one suitable control was identified, and no control could be allocated in seven cases.

Data collection

This retrospective evaluation of data was approved by the Ethics Committee of the Medical Faculty, University of Würzburg (protocol number #5/14). A thorough clinical history was taken following a standardized questionnaire. Baseline clinical data (age, sex, clinical signs and symptoms of BP, comorbidities, concomitant medication) and diagnostic results (direct immunofluorescence and anti-BP180 antibodies, laboratory values) were retrospectively retrieved from the medical records. Documentation was focused on, but not limited to psychiatric and neurological disorders, skin diseases, malignancy, cardiovascular and renal conditions, diabetes mellitus and hematological disorders.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY). Due to the matching procedure the results of BP patients and controls were considered as dependent variables. Hence, conditional logistic regression was performed to compare data of BP patients and controls. It was conducted for (1) all parameters that were available in more than half of the patients and controls, (2) for all diseases that were documented in at least five BP patients and (3) and for all comorbidities that were more frequent in terms of percentage in BP patients compared to controls. Odds ratio (OR), 95 % confidence interval (CI) and p-value were calculated. The cut-off p-value for statistical significance was 0.05, p-values < 0.001 indicate statistically highly significant results. Sometimes, subsequently to univariate analyses, unplanned exploratory multivariable ad hoc analyses were performed. The resulting p-values are, as all p-values presented here, exploratory p-values, all analysis is without controlling Type I error rate. That means, for selected significant findings i.e. anemia (defined as hemoglobin below normal levels), renal impairment (defined as elevated creatinine), diabetes mellitus, neuropsychiatric diseases and depression, further investigation was performed by multivariable logistic regression analysis. Prior to this, contingency tables were generated, and Fisher's exact test was conducted for all other significant findings ($p < 0.05$). Finally, complex regression models were used to investigate significant associations taking several probable confounders into account.

Results

Three hundred patients and 583 controls were analyzed (Table 1). According to the matching criteria 17 controls could not been identified. The mean age was 78.6 ± 11.2 years (median 81 years) for BP patients and 77.9 ± 11.0 years (median 80 years) for the matched controls. The youngest BP patient was 34, the eldest 100 years old. 136 male patients (45.3 %) and 164 female patients (54.7 %) were analyzed in the BP group compared to 271 males (46.5 %) and 312 females (53.5 %) in the control group.

Table 2 summarizes the significant results of conditional logistic regression analysis. Significant differences were detected for leukocytosis (BP patients: 41.7 %, n = 120; controls: 12.9 %, n = 73; OR 4.371, CI 3.034–6.296, p < 0.0005) and eosinophilia (BP patients: 66.9 %, n = 170; controls: 5.9 %, n = 23; OR 64.783, CI 20.477–204.959, p < 0.0005). Notably, there was a strong association with anemia (BP patients: 39.8 %, n = 115; controls: 25.0 %, n = 141; OR 2.127,

Table 1 Demographic features and autoimmunological findings of BP patients and controls.

	BP patients (n = 300)	Controls (n = 583)
Gender (n (%))		
Female	164 (54.7 %)	312 (53.5 %)
Male	136 (45.3 %)	271 (46.5 %)
Age (years)		
< 40	2 (0.7 %)	4 (0.7 %)
40–49	6 (2.0 %)	13 (2.2 %)
50–59	9 (3.0 %)	17 (2.9 %)
60–69	33 (11.0 %)	70 (12.0 %)
70–79	83 (27.7 %)	166 (28.5 %)
80–89	130 (43.3 %)	257 (44.1 %)
> 89	37 (12.3 %)	56 (9.6 %)
DIF (n (%))		
Positive	228 (76.0 %)	N/A
Negative or unspecific	32 (10.7 %)	N/A
Not performed	40 (13.3 %)	583 (100 %)
Anti-BP180 AB (ELISA)		
Positive	268 (89.3 %)	N/A
Negative	30 (10.0 %)	N/A
Not performed	2 (0.7 %)	N/A

Abbr.: AB, antibody; BP, bullous pemphigoid; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; N/A, not available.

CI 1.532–2.953, p < 0.0005). Further analysis revealed that normocytic normochromic anemia was the predominant form of anemia within the group of BP patients (90 of 115 [78.3 %]; for detailed analysis of anemia in BP patients see Online Supplementary Table S1).

In addition, elevated erythrocyte sedimentation rate and thrombocytosis were more frequently observed in BP patients.

In 20.3 % (n = 61) of the 300 BP patients, a psychiatric disease was documented, compared to only 9.3 % (n = 54) in controls (OR 2.441, CI 1.647–3.619, p < 0.0005). In addition, neurological diseases were overrepresented in BP patients (49.0 %; n = 147) compared to controls (23.0 %, n = 134, OR 3.591, CI 2.564–5.029, p < 0.0005). In detail, 67 BP patients (22.3 %) had a history of previous stroke (controls: 11.0 %; n = 64; OR 2.355, CI 1.605–3.456, p < 0.0005), 42 patients (14.0 %) suffered from depression (controls: 8.2 %; n = 48; OR 1.799, CI 1.155–2.803, p < 0.05),12 patients (4.0 %) from organic brain syndrome (controls: 0.7 %; n = 4; OR 5.500, CI 1.751–17.273, p < 0.05), 5 patients (1.7 %) from multiple sclerosis (controls: 0.2 %; n = 1; OR 10.000, CI 1.168–85.594, p < 0.05), 15 patients (5.0 %) from epilepsy (controls: 2.2 %; n = 13; OR 2.397, CI 1.117–5.142, p < 0.05), 83 patients (27.7 %) from dementia (controls: 5.8 %; n = 34; OR 7.475, CI 4.456–12.540, p < 0.0005), 22 patients (7.3 %) from Parkinson´s disease (controls: 2.6 %; n = 15; OR 3.033, CI 1.510–6.089, p < 0.05). No significant difference between BP patients and controls could be observed with regard to schizophrenia.

The frequency of a former or current diagnosis of malignancy (excluding skin cancer) was slightly higher in BP patients (15.7 %, n = 47) compared to controls (12.9 %, n = 75). Further analysis revealed an increased prevalence for prostate cancer (BP patients: 4.7 %, n = 14; controls: 3.8 %, n = 22) and renal cancer (BP patients: 1.7 %, n = 5; controls: 0.9 %, n = 5). However, these findings were not significant.

Diabetes mellitus was significantly more frequent in BP patients compared to controls. No association was found with arterial hypertension (BP patients: 74 %, n = 222; controls: 72.6 %, n = 423; OR 1.109, CI 0.797–1.542, p = 0.54).

An elevated serum creatinine (BP patients: 51.0 %, n = 146; controls: 31.4 %, n = 177; OR 2.218, CI 1.643–2.993, p < 0.0005) was commonly found in BP patients and detailed analysis showed an increased frequency of chronic renal insufficiency stage IV (BP patients: 7.3 %, n = 22; controls: 1.7 %, n = 10; OR 3.445, CI 1.384–8.574, p < 0.05). No significant differences between BP patients and controls were detected regarding liver enzymes.

Anemia, renal impairment, diabetes mellitus, depression and neuropsychiatric diseases were selected for further statistical investigation by multivariable analysis (Online Supplementary Table S2). These associations were chosen *(1)* due to sufficient prevalence in BP and control patients, and *(2)* considering results of previous studies. After adjustment for confounders a significant association of BP with anemia, renal impairment, neurologic and psychiatric diseases (any) was still detectable (Online Supplementary Table S2). The associations for neurologic and psychiatric diseases were reconfirmed in the final complex multivariable regression model (Table 3).

Discussion

The strengths of our study are the relative large sample size (300 BP patients) and multivariable statistical evaluation including comparison to 583 matched controls. The diagnosis of BP was based on established criteria [15] taking into account clinical features as well as the results of immunofluorescence. Comorbid diseases were not only identified by

Table 2 Significant associations of comorbid diseases in BP patients compared to controls.

Comorbidity	BP patients, % (n) n = 300	controls, % (n) n = 583	OR	95 % CI	p-value
Neuropsychiatric disorders					
Neurologic disorder (any)	49.0 % (147)	23.0 % (134)	3.591	2.564–5.029	< 0.0005
Stroke	22.3 % (67)	11.0 % (64)	2.355	1.605–3.456	< 0.0005
Dementia	27.7 % (83)	5.8 % (34)	7.475	4.456–12.540	< 0.0005
Parkinson's disease	7.3 % (22)	2.6 % (15)	3.033	1.510–6.089	0.002
Multiple sclerosis	1.7 % (5)	0.2 % (1)	10.000	1.168–85.594	0.036
Epilepsy	5.0 % (15)	2.2 % (13)	2.397	1.117–5.142	0.025
Psychiatric disorder (any)	20.3 % (61)	9.3 % (54)	2.441	1.647–3.619	< 0.0005
Depression	14.0 % (42)	8.2 % (48)	1.799	1.155–2.803	0.009
Organic brain syndrome	4.0 % (12)	0.7 % (4)	5.500	1.751–17.273	0.004
Other diseases					
Diabetes mellitus	30.0 % (90)	23.2 % (135)	1.418	1.037–1.939	0.029
Laboratory findings					
Leukocytosis	41.7 % (120)	12.9 % (73)	4.371	3.034–6.296	< 0.0005
Eosinophilia	66.9 % (170)	5.9 % (23)	64.783	20.477–204.959	< 0.0005
Thrombocytosis	4.9 % (14)	1.1 % (6)	4.446	1.572–12.579	0.005
Anemia	39.8 % (115)	25.0 % (141)	2.127	1.532–2.953	< 0.0005
Elevated erythrocyte sedimentation rate	42.3 % (66)	27.5 (85)	1.838	1.109–3.044	0.018
Kidney failure (acute and/or chronic)	51.0 % (146)	31.4 % (177)	2.218	1.643–2.993	< 0.0005

Abbr.: BP, bullous pemphigoid. CI, confidence interval; OD, odds ratio.

diagnostic codes but verified by laboratory findings and a thorough investigation of clinical records. The study's main limitation is its retrospective approach. Certain comorbid diseases (e.g. organic brain syndrome) could not be included in the multivariable statistical models due to their relative infrequence. For practical reasons such as the availability of information concerning comorbidity and laboratory findings, control individuals were identified within patients that had been referred to our department for surgery of basal cell carcinoma. Therefore, selection bias cannot be excluded and comparability to other case-controlled studies may be limited.

The potential association between BP and malignancies has been discussed extensively [9, 11, 12, 16–25]. Results of previous studies, however, are inconsistent. Several studies are restricted to descriptive observations [17, 23]. Seven studies including a comparative statistic evaluation did not confirm an association between malignancy and BP [11, 12, 16, 20, 22, 24, 26]. One retrospective case-control study from China described an increased incidence of malignancy in BP patients [18]. Ong et al. did not observe an association of BP with malignancy *per se*, but found an association for kidney cancer, laryngeal cancer and lymphoid leukemia [19]. In accordance with these results, Schulze et al. described an association of BP with hematological malignancies [21]. More recently, a study from Finland showed an increase of solid tumors and hematological diseases in BP patients compared to an age-matched control population [25]. In summary, interpretation of the available studies remains difficult, due to the diversity and heterogeneity of malignant conditions.

In the present study, we could not detect an association between malignancies and BP. No conclusions could be made with regard to non-melanoma cancer of the skin as the controls were selected from a group of patients undergoing surgery for basal cell carcinoma.

Table 3 Results of complex multivariable regression model analysis.

Comorbidity	Confounder	OR	95 % CI	p-value
Anemia	– Neurologic disorder (any) – Stroke – Dementia – Parkinson's disease – Leukocytosis – Thrombocytosis – Eosinophilia – Elevated erythrocyte sedimentation rate – Kidney failure (acute and/or chronic)	1.752	0.965–3.181	0.065
Kidney failure (acute and/or chronic)	– Neurologic disorder (any) – Stroke – Dementia – Parkinson's disease – Diabetes mellitus type 2 – Anemia – Leukocytosis – Eosinophilia – Elevated erythrocyte sedimentation rate	1.594	0.918–2.768	0.098
Diabetes mellitus type 2	– Neurologic disorder (any) – Stroke – Dementia – Parkinson's disease – Leukocytosis – Kidney failure (acute and/or chronic)	0.894	0.603–1.324	0.575
Neurologic disorder (any)	– Psychiatric disorder (any) – Depression – Diabetes mellitus type 2 – Anemia – Leukocytosis – Eosinophilia – Elevated erythrocyte sedimentation rate – Kidney failure (acute and/or chronic)	2.025	1.177–3.483	0.011
Psychiatric disorder (any)	– Neurologic disorder (any) – Dementia – Parkinson's disease – Eosinophilia	2.898	1.506–5.577	0.001
Depression	– Dementia – Parkinson's disease	1.530	0.937–2.498	0.089

Abbr.: CI, confidence interval; OD, odds ratio.

BP180, the main BP autoantigen, is not only expressed in the hemidesmosomes of the basal membrane of the skin but also in other tissues including the brain [6, 27]. In addition, neuronal isoforms of BP230 exist [28]. In serum samples of BP patients with neurological diseases, autoantibodies recognizing a 230-kDa protein of human brain extract were detected [28]. Cross-reaction with BP230 of the skin was postulated. Alteration of the blood-brain barrier, as it is seen in some neurological diseases [29], might also favor the development of BP and is a possible explanation for the association between BP with different neurological and psychiatric disorders [28]. Association with multiple sclerosis, dementia,

Parkinson´s disease, epilepsy and cerebrovascular disorders was demonstrated and confirmed by several studies [6–13]. Our findings were in line with these results. In our cohort, we found hints to associations with Parkinson´s disease, multiple sclerosis, epilepsy, depression and organic brain syndrome and a highly significant association with stroke and dementia.

Some smaller studies from the 1980s and 1990s reported an increased frequency of diabetes mellitus in BP patients [5, 30]. However, these results were not confirmed by subsequent studies [10, 12, 16, 18, 22, 26, 31]. In recent years, the focus was redirected to a potential association of BP with diabetes mellitus as a result of the discussion if dipeptidyl peptidase-4 (DPP-4) inhibitors may promote the development of BP [32–35]. Since 2006, more than 10 DPP-4 inhibitors were approved. Pharmacovigilance databases indicated an increased risk of BP for patients taking DPP-4 inhibitors. The likelihood to trigger BP might differ within the group of gliptins [35, 36]. In our study, significantly more BP patients suffered from diabetes mellitus compared to controls. As we did not review medication in detail, the potential influence of DPP-4 inhibitors on these results could not be estimated.

Although slightly more BP patients had a history of arterial hypertension compared to controls, we could not demonstrate a statistically significant association. These results are in contrast to a recently published case-control study of 218 BP patients by Kalinska-Bienias et al., who demonstrated a strong association between arterial hypertension and BP in Polish patients [9]. Nevertheless, data of the available studies are inconsistent [13].

Little is known about the association of renal impairment and BP. A recent case-control study showed a significant association of chronic kidney disease and end-stage renal disease with BP [14]. In our study, kidney failure was more frequent in BP patients compared to controls. These results were highly significant in multivariable analysis but failed to be significant in the final complex multivariable regression model. One might speculate that the burden of BP, which – in our experience – often leads to a deterioration of the general condition in BP patients, might explain an acute aggravation of the renal function. More objective information regarding the patients' general condition including Karnofsky Performance Status Scale, might help to corroborate this hypothesis. In addition, differentiation between acute and chronic renal failure is necessary. As kidney function was classified depending on the serum creatinine value and the glomerular filtration rate at a defined time point, our data do not provide this information. Chronic kidney disease or an acute aggravation of chronic renal impairment influences drug metabolism. As a consequence, it seems possible that these changes may contribute to BP development in susceptible individuals [37].

It is well known that eosinophils play an important role in the pathogenesis of BP [38–40]. One key feature in histopathology is a strong eosinophilic inflammatory infiltrate. Peripheral blood eosinophilia is observed in about 50–60 % of BP patients [38, 39]. Our findings are consistent with these results, 66.9 % of our patients showed elevated absolute numbers of eosinophils in the peripheral blood. In this context, it is hardly surprising that in 41.7 % of BP patients leukocytosis was detected as well. The total increase of white blood cells thus probably results from excessive eosinophilia, but independent triggers of leukocytosis including previous treatment with topical or systemic glucocorticoids need to be considered.

Thrombocytosis is a frequent condition that could occur within a clonal process but is much more frequently observed within chronic inflammatory diseases, acute infections, tissue damage or malignancy [41]. One could speculate that reactive thrombocytosis is frequent in BP but, as far as we know, no data are available. In the present study, 4.9 % of our BP patients revealed thrombocytosis as compared to 1.1 % of control patients which was statistically significant.

Up to now, anemia has not been in the focus as comorbid disease of BP. Only two studies investigated anemia in BP patients [14, 42]. Ren et al. analyzed data records from a national database that covered 20 % of all hospitalizations in the USA. The authors considered ICD-9-CM diagnostic codes and found a significant association between BP and deficiency anemia but not for anemia of chronic disease [42]. Recently, a case-control study of 91 BP patients did not show an increased frequency of anemia compared to controls [14]. We here showed that anemia is more frequent in BP patients, although these results failed to be significant the final complex multivariable regression model. Anemia could be the result of various underlying conditions including but not limited to malignancies, gastrointestinal bleeding, hemolysis, iron or vitamin B12 deficiency, renal failure or chronic diseases. Our findings could not be explained by a higher frequency of malignancies, as no difference was observed between the two analyzed groups. Moreover, use of dapsone, a drug commonly used in BP treatment that frequently leads to drop of hemoglobin [43], as cause of anemia could be widely excluded as data were collected at the time point when diagnosis of BP was first established and dapsone yet not prescribed.

A more detailed analysis of the different subtypes of anemia in BP patients revealed that normocytic normochromic anemia was predominant. Characterization of the underlying pathomechanisms was not possible in detail, as further laboratory results such as serum iron, ferritin, transferrin and/or soluble transferrin receptor had not been determined regularly and, therefore, were not available. Since the majority (74.4 %; data not shown) of BP patients with normocytic normochromic anemia also suffered from renal impairment

it may be speculated that chronic kidney disease could be responsible for a considerable number of the anemia cases. This interpretation is supported by the results of the final complex multivariable regression model that did not confirm a significant association of anemia in BP patients when considering various confounders including kidney failure.

On the other hand, chronic inflammation, potentially in combination with renal impairment, may be another cause of anemia (anemia of chronic inflammation, formerly termed anemia of chronic disease). Notably, we also observed an association with leukocytosis, thrombocytosis and elevated erythrocyte sedimentation rate that might be due to a BP-associated systemic inflammatory response. In this context, evaluation of other inflammatory markers, such as C-reactive protein (CRP) would have been desirable; however, CRP values had not routinely been determined in the basal cell carcinoma patients of our control group and could thus not been considered for case-control analysis. In any case, additional laboratory studies are necessary to clarify this point.

Conclusions

This large case-control study of BP patients in Germany confirmed results from previous investigations showing a strong association with neuropsychiatric disorders. The observation of increased frequency of renal impairment and the association of anemia with BP should be reconfirmed in independent patient cohorts.

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References

1 Hübner F, Recke A, Zillikens D et al. Prevalence and age distribution of pemphigus and pemphigoid diseases in Germany. J Invest Dermatol 2016; 136: 2495–8.
2 Sadik CD, Schmidt E. Resolution in bullous pemphigoid. Semin Immunopathol 2019; 41: 645–54.
3 Callen JP. Internal disorders associated with bullous disease of the skin. A critical review. J Am Acad Dermatol 1980; 3: 107–19.
4 Dahl MV. Bullous pemphigoid: associated diseases. Clin Dermatol 1987; 5: 64–70.
5 Rosina P, Chieregato C, D'Onghia FS. Bullous pemphigoid and diabetes mellitus. Acta Derm Venereol 1996; 76: 497–8.
6 Forsti AK, Huilaja L, Schmidt E et al. Neurological and psychiatric associations in bullous pemphigoid-more than skin deep? Exp Dermatol 2017; 26: 1228–34.
7 Kibsgaard L, Rasmussen M, Lamberg A et al. Increased frequency of multiple sclerosis among patients with bullous pemphigoid: a population-based cohort study on comorbidities anchored around the diagnosis of bullous pemphigoid. Br J Dermatol 2017; 176: 1486–91.
8 Papakonstantinou E, Limberg MM, Gehring M et al. Neurological disorders are associated with bullous pemphigoid. J Eur Acad Dermatol Venereol 2019; 33: 925–9.
9 Kalinska-Bienias A, Kowalczyk E, Jagielski P et al. The association between neurological diseases, malignancies and cardiovascular comorbidities among patients with bullous pemphigoid: Case-control study in a specialized Polish center. Adv Clin Exp Med. 2019; 28: 637–42.
10 Bastuji-Garin S, Joly P, Lemordant P et al. Risk factors for bullous pemphigoid in the elderly: a prospective case-control study. J Invest Dermatol 2011; 131: 637–43.
11 Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: a population-based case-control study. J Invest Dermatol 2011; 131: 631–6.
12 Teixeira VB, Cabral R, Brites MM et al. Bullous pemphigoid and comorbidities: a case-control study in Portuguese patients. An Bras Dermatol 2014; 89: 274–8.
13 Bech R, Kibsgaard L, Vestergaard C. Comorbidities and treatment strategies in bullous pemphigoid: an appraisal of the existing literature. Front Med (Lausanne) 2018; 5: 238.
14 Lee S, Rastogi S, Hsu DY et al. Association of bullous pemphigoid and comorbid health conditions: a case-control study. Arch Dermatol Res 2021; 313(5): 327–32.
15 Schmidt E, Goebeler M, Hertl M et al. S2k guideline for the diagnosis of pemphigus vulgaris/foliaceus and bullous pemphigoid. J Dtsch Dermatol Ges 2015; 13: 713–27.
16 Jedlickova H, Hlubinka M, Pavlik T et al. Bullous pemphigoid and internal diseases – A case-control study. Eur J Dermatol 2010; 20: 96–101.
17 Kibsgaard L, Bay B, Deleuran M et al. A retrospective consecutive case-series study on the effect of systemic treatment, length of admission time, and co-morbidities in 98 bullous pemphigoid patients admitted to a tertiary centre. Acta Derm Venereol 2015; 95: 307–11.
18 Li J, Zuo YG, Zheng HY et al. Association between bullous pemphigoid and internal diseases. J Dtsch Dermatol Ges 2013; 11: 263–4.
19 Ong E, Goldacre R, Hoang U et al. Associations between bullous pemphigoid and primary malignant cancers: an English national record linkage study, 1999–2011. Arch Dermatol Res 2014; 306: 75–80.
20 Cai SC, Allen JC, Lim YL et al. Association of Bullous Pemphigoid and Malignant Neoplasms. JAMA Dermatol 2015; 151: 665–7.
21 Schulze F, Neumann K, Recke A et al. Malignancies in pemphigus and pemphigoid diseases. J Invest Dermatol 2015; 135: 1445–7.

22 Kwan Z, Lai YN, Ch'ng CC et al. The association between bullous pemphigoid and neurological disorders in a selected Malaysian population. Med J Malaysia 2015; 70: 81–5.
23 Ogawa H, Sakuma M, Morioka S et al. The incidence of internal malignancies in pemphigus and bullous pemphigoid in Japan. J Dermatol Sci 1995; 9: 136–41.
24 Wright B, Halper K, Worswick S. Bullous pemphigoid and malignancy in two different hospital populations: a retrospective cohort review. Oncology 2020; 98: 318–20.
25 Pankakoski A, Sintonen H, Ranki A et al. Comorbidities of bullous pemphigoid in a Finnish cohort. Eur J Dermatol 2018; 28: 157–61.
26 Casas-de-la-Asuncion E, Ruano-Ruiz J, Rodriguez-Martin AM et al. Association between bullous pemphigoid and neurologic diseases: a case-control study. Actas Dermosifiliogr 2014; 105: 860–5.
27 Seppanen A, Autio-Harmainen H, Alafuzoff I et al. Collagen XVII is expressed in human CNS neurons. Matrix Biol 2006; 25: 185–8.
28 Chen J, Li L, Zeng Y et al. Sera of elderly bullous pemphigoid patients with associated neurological diseases recognize bullous pemphigoid antigens in the human brain. Gerontology 2011; 57: 211–6.
29 Barnes D, Munro PM, Youl BD et al. The longstanding MS lesion. A quantitative MRI and electron microscopic study. Brain 1991; 114 (Pt 3): 1271–80.
30 Chuang TY, Korkij W, Soltani K et al. Increased frequency of diabetes mellitus in patients with bullous pemphigoid: a case-control study. J Am Acad Dermatol 1984; 11: 1099–102.
31 Taylor G, Venning V, Wojnarowska F et al. Bullous pemphigoid and autoimmunity. J Am Acad Dermatol 1993; 29: 181–4.
32 Fania L, Di Zenzo G, Didona B et al. Increased prevalence of diabetes mellitus in bullous pemphigoid patients during the last decade. J Eur Acad Dermatol Venereol 2018; 32: e153–e54.
33 Fania L, Di Zenzo G, Mazzanti C et al. Commentary on 'Changing prevalence of diabetes mellitus in bullous pemphigoid: it is the dipeptidyl peptidase-4 inhibitors'. J Eur Acad Dermatol Venereol 2018; 32: e439–e40.
34 Gravani A, Gaitanis G, Tsironi T et al. Changing prevalence of diabetes mellitus in bullous pemphigoid: it is the dipeptidyl peptidase-4 inhibitors. J Eur Acad Dermatol Venereol 2018; 32: e438–9.
35 Kridin K. Dipeptidyl-peptidase IV inhibitors (DPP4i)-associated bullous pemphigoid: Estimating the clinical profile and exploring intraclass differences. Dermatol Ther 2020; 33: e13790.
36 Nishie W. Dipeptidyl peptidase IV inhibitor-associated bullous pemphigoid: a recently recognized autoimmune blistering disease with unique clinical, immunological and genetic characteristics. Immunol Med 2019; 42: 22–8.
37 Sanchez Lopez-Muelas B, Muray Cases S, Illan Gomez F et al. Bullous pemphigoid associated with linagliptin treatment in diabetic patients with chronic kidney disease. Endocrinol Diabetes Nutr 2019; 66: 338–9.
38 Bernard P, Venot J, Constant F et al. Blood eosinophilia as a severity marker for bullous pemphigoid. J Am Acad Dermatol 1987; 16: 879–81.
39 Bushkell LL, Jordon RE. Bullous pemphigoid: a cause of peripheral blood eosinophilia. J Am Acad Dermatol 1983; 8: 648–51.
40 van Beek N, Schulze FS, Zillikens D et al. IgE-mediated mechanisms in bullous pemphigoid and other autoimmune bullous diseases. Expert Rev Clin Immunol 2016; 12(3): 267–77.
41 Bleeker JS, Hogan WJ. Thrombocytosis: diagnostic evaluation, thrombotic risk stratification, and risk-based management strategies. Thrombosis. 2011; 2011: 536062.
42 Ren Z, Hsu DY, Brieva J et al. Hospitalization, inpatient burden and comorbidities associated with bullous pemphigoid in the U.S.A. Br J Dermatol 2017; 176: 87–99.
43 Eming R, Sticherling M, Hofmann SC et al. S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid. J Dtsch Dermatol Ges 2015; 13: 833–44.

