The association between neurological diseases, malignancies and cardiovascular comorbidities among patients with bullous pemphigoid: Case-control study in a specialized Polish center

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Abstract

Background. Bullous pemphigoid (BP) is the most common autoimmune bullous disease associated with higher mortality and coexisting comorbidities. The strongest relationship has been reported with neurological diseases (NDs) but the particular type of ND differed depending on the study. There are some doubts on the prevalence of other comorbidities.

Objectives. The aim of this study was to compare the incidence of various comorbidities in a cohort of BP patients with controls.

Material and methods. A cohort of 218 patients (137 females, 81 males, aged 76.2 ±11.6 years) with newly diagnosed BP who were hospitalized at a specialized center in Poland in the years 2000–2014 was included in this retrospective study. The controls consisted of 168 sex- and age-matched individuals. Univariate and multivariate logistic regression analyses were performed to assess the association between the groups studied.

Results. At least 1 ND was present in 33.5% of BP patients vs 11.3% of controls. A strong association between the incidence of NDs and BP was found (OR = 3.76; 95% CI = 2.13–6.65; $p < 0.001$), especially for dementia (20.6% vs 2.9%, OR = 7.89; 95% CI = 2.99–20.85; $p < 0.001$). Surprisingly, BP patients with ND were older than the BP patients without ND (79.2 vs 74.7 years), and similarly for dementia (81.08 vs 74.90 years). The same was observed in comparison with controls. Arterial hypertension, among other comorbidities, was a strong independent factor associated with BP (OR = 2.17; 95% CI = 1.35–3.49; $p < 0.001$). Malignancies were observed more frequently in BP patients than in controls (12.8% vs 9%) but such association was significant in univariate analysis only.

Conclusions. Neurological diseases, particularly dementia, had a significant association with BP. A strong relationship with arterial hypertension and weak relationship with malignancies were noted. Thus, for appropriate medical care, patients with BP need accurate screening for dementia and control of comorbidities with interdisciplinary management.

Key words: comorbidities, neurological diseases, bullous pemphigoid, internal diseases

Introduction

Bullous pemphigoid (BP) is the most common autoimmune bullous disorder caused by autoantibodies directed against BPA2 (BP180) and BPA1 (BP230) proteins located in the basement membrane zone (BMZ). Clinically it is characterized by tense bullae, urticarial skin lesions and pruritus, primarily affecting elderly individuals, with risk increasing with age.[1,2] The worldwide incidence ranges from 6.6 to 42.8 new cases per million people yearly while in Poland the BP incidence is estimated at 7 per million inhabitants per year. Bullous pemphigoid is a potentially fatal disease with 1-year and 3-year mortality rates assessed at 22.4% and 39.5%, respectively, in Polish BP patients.[3,4]

In recent years, many epidemiological studies have investigated the coexistence of BP with various comorbidities. In fact, the most intense research has been focused on neurological diseases (NDs), showing that BP patients are more likely to have any type of ND.[2,5–7] However, the particular types of ND among BP patients differed depending on the study and some results were even conflicting.[1,2,5,6,8–13] Some data found a higher prevalence of stroke, dementia, Parkinson's disease, epilepsy, and multiple sclerosis in BP.[1,2,5,6,8–14] Other studies have also identified psychiatric diseases such as schizophrenia, personality or unipolar/bipolar disorders as a risk factor for BP.[6,15] Moreover, some studies have referred to the incidence of malignancies in BP patients, with some showing a higher proportion in BP patients.[16–19] In spite of this, the debate is ongoing and this relationship remains controversial. There are several publications in the literature that have reported a higher prevalence of arterial hypertension in BP patients. The fact is that this disease may play an important role in BP patients, especially since major drugs used to treat hypertension such as diuretics, ACE inhibitors or spironolactone can provoke BP.[6,13,20–22] Among other comorbidities, single studies have demonstrated the association of BP with diabetes.[23–25]

To confirm or reject the abovementioned discrepancies, the aim of this study was to assess the relationship between BP and selected comorbidities. The groups of NDs (dementia, stroke, Parkinson's disease, epilepsy, multiple sclerosis, and depression), cardiovascular diseases (arterial hypertension, arrhythmia, coronary artery disease, heart failure, and thromboembolic syndrome), malignancies, and diabetes mellitus were included.

Material and methods

The patients were diagnosed and treated in the Department of Dermatology and Immunodermatology at the Medical University of Warsaw (Poland) in the period 2000–2014. The retrospectively-assessed group consisted of 386 persons (218 BP patients and 168 controls). The BP diagnosis was based on clinical features and positive direct immunofluorescence (DIF) of perilesional skin (linear IgG and/or C3 deposits along the BMZ). Additionally, indirect immunofluorescence (IIF) detecting circulating anti-BMZ antibodies and/or examination of salt split skin and/or enzyme-linked immunosorbent assay (ELISA) for anti-BP180 NC16a (MESACUP BP 180 ELISA kit; Medical&Biological Laboratories, Nagoya, Japan) were performed. In the group studied, almost all BP patients were positive for circulating autoantibodies (in 95.7%).

The controls were randomly selected from patients admitted in the same period due to other dermatological diseases such as eczema, drug eruptions, erysipelas, herpes zoster, leg ulcers, urticaria, atopic dermatitis, scabies, erythema multiforme, lichen planus, or pityriasis rubra pilaris. Subjects with dermatological diseases characterized by systemic symptoms (e.g., connective tissue disorders, psoriasis, lymphoma) were not included to the control group. The diagnosis of particular additional diseases was based on a reliable anamnesis or medical documentation including the results of appropriate tests. If any uncertainty was present, a cardiologist and/or a neurologist was asked for a medical consultation to confirm or reject a diagnosis.

Approval from the local Ethics Committee of the Medical University of Warsaw was obtained before starting the study.

Statistical analysis

The patients with BP and controls were compared using either the Student's t-test or the Wilcoxon test according to the parameters of distribution assessed with the Kolmogorov-Smirnov test. Variables with a normal distribution are presented as a mean followed by standard deviation (SD). Variables not showing the normal distribution are presented as a median with range values. For categorical variables, the differences between groups were compared using the exact Fisher test. All tests were double-sided. Correlations were evaluated using Spearman correlation coefficients. Crude and adjusted odds ratios (OR) and a 95% confidence interval (95% CI) were estimated using univariate and multivariate logistic regression analyses for both groups. An association model was constructed using BP diagnosis as the dependent variable. Values of $p < 0.05$ were considered statistically significant. Analyses were performed using a statistical software package (STATISTICA v. 12; StatSoft Inc., Tulsa, USA).

Results

Among the cohort of 218 BP patients, 137 (62.8%) were female and 81 (37.2%) were male. In the 168 controls there were 101 (60.1%) females and 67 (39.9%) males. Mean age at BP diagnosis was 76.2 ±11.62 years, median 78 years (range: 33–100 years); and mean age for the controls was 75 ±10.92 years, median 77 years (range: 33–92 years). The BP patients and controls were age- and gender-matched (Table 1).

Table 1. Univariate and multivariate regression analysis of comorbidities influencing bullous pemphigoid and controls

Variable	BP patients n = 218 [%]	Controls n = 168 [%]	p-value	Univariate analysis in BP patients		Multivariate analysis in BP patients			
				[a]OR (95% CI)	p-value	[b]OR (95% CI)	p-value	[c]OR (95% CI)	p-value
Gender: female	137 (62.8)	101 (60.1)	0.60	–	–	–	–	–	–
Age [years]	76.23 ±11.62	75.03 ±10.92	0.30	–	–	–	–	–	–
Any neurological disease	73 (33.5)	19 (11.3)	<0.001	3.95 (2.26–6.89)	<0.001	3.67 (2.05–6.55)	<0.001	3.76 (2.13–6.65)	<0.001
Dementia	45 (20.6)	5 (2.9)	<0.001	8.48 (3.27–21.9)	<0.001	7.86 (2.94–21.03)	<0.001	7.89 (2.99–20.85)	<0.001
Stroke	28 (12.8)	9 (5.3)	0.01	2.60 (1.19–5.69)	0.01	2.12 (0.91–4.94)	0.08	2.18 (0.95–4.98)	0.06
Parkinson's disease	11 (5)	3 (1.7)	0.1	2.92 (0.80–10.69)	0.1	3.03 (0.74–12.32)	0.11	–	–
Multiple sclerosis	1 (0.5)	1 (0.6)	1.0	0.77 (0.04–12.50)	0.85	1.05 (0.06–17.92)	0.97	–	–
Epilepsy	1 (0.5)	1 (0.6)	1.0	0.77 (0.04–12.50)	0.85	0.86 (0.05–14.46)	0.91	–	–
Arterial hypertension	166 (76.1)	100 (59.2)	<0.001	2.17 (1.40–3.37)	<0.001	2.16 (1.31–3.73)	0.002	2.17 (1.35–3.49)	0.001
Stable coronary artery disease	82 (37.6)	48 (28.5)	0.06	1.51 (0.98–2.33)	0.06	1.29 (0.77–2.15)	0.32	–	–
Myocardial infarction	16 (7.3)	12 (7.1)	1.0	1.03 (0.47–2.23)	0.94	0.84 (0.34–2.08)	0.71	–	–
Thromboembolic events	13 (5.9)	4 (2.3)	0.13	2.6 (0.83–8.15)	0.1	2.51 (0.71–8.80)	0.14	–	–
Arrhythmias	46 (21.1)	26 (15.4)	0.18	1.46 (0.86–2.48)	0.16	1.40 (0.79–2.50)	0.24	–	–
Malignancies	32 (14.6)	13 (7.7)	0.03	2.05 (1.03–4.60)	0.03	1.74 (0.84–3.65)	0.13	1.92 (0.94–3.96)	0.07
Diabetes mellitus	47 (21.5)	33 (19.6)	0.70	0.64 (0.68–1.85)	0.64	0.97 (0.54–1.72)	0.91	–	–

[a]crude OR (95% CI), [b]adjusted OR (95% CI) to age and gender, analyzed to all variables, [c]adjusted OR (95% CI) analyzed to significant values; BP – bullous pemphigoid; OR – odds ratio.

Neurological diseases

At least 1 ND was found in 73 BP patients (33.5%) and in 19 controls (11.3%). The significant association between BP and the incidence of NDs was confirmed in multivariate regression analysis (OR = 3.76, 95% CI = 2.13–6.65, p < 0.001) (Table 1). Thirteen BP patients (6%) had 2 NDs in comparison with none in the controls. The mean age of BP patients with ND was 79.2 vs 74.7 years in patients without ND. The same was observed in comparison with controls (Table 2). The most frequent ND in BP was dementia, which was observed in 45 (20.6%) patients, followed by stroke in 28 (12.8%), Parkinson's disease in 11 (5%), epilepsy in 1 patient, and multiple sclerosis in 1 other patient. In the controls, stroke was the most frequently observed ND in 9 (5.3%) subjects, followed by dementia in 5 (2.9%), Parkinson's disease in 3 (1.7%), epilepsy in 1, and multiple sclerosis in 1 individual. The BP patients had a significantly increased risk for dementia (OR = 8.48, 95% CI = 3.27–21.90, p < 0.001) and stroke (OR = 2.60, 95% CI = 1.19–5.69, p = 0.01) assessed by univariate analysis, whereas only dementia remained statistically significant in multivariate regression analysis (OR = 7.89, 95% CI = 2.99–20.85, p < 0.001) (Table 1). A statistically higher age for BP patients with dementia vs without was observed (81.1 vs 74.97 years, p = 0.001) (Fig. 1).

Table 2. Age of BP patients and controls with and without selected comorbidities

Variable	Age		p-value
	BP patients	controls	
Neurological disease			
yes	79.21 ±7.50	76.15 ±9.85	0.14
no	74.73 ±12.99	74.89 ±11.07	0.91
Dementia			
yes	81.08 ±7.32	73.80 ±16.42	0.07
no	74.97 ±12.21	75.07 ±10.78	0.93
Stroke			
yes	77.67 ±7.89	74.77 ±7.89	0.34
no	76.02 ±12.08	75.05 ±11.08	0.44
Arterial hypertension			
yes	78.00 ±10.22	75.88 ±10.08	0.10
no	70.59 ±13.95	73.79 ±12.01	0.18
Malignancies			
yes	77.81 ±9.87	72.15 ±10.88	0.09
no	75.96 ±11.90	75.27 ±10.92	0.58

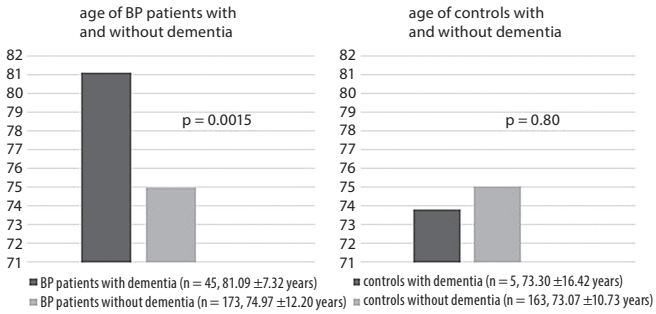

Fig. 1. Age of bullous pemphigoid (BP) patients and controls with and without dementia

Malignancies

A history of malignancies was recognized in 32 BP patients (14.6%) and 13 controls (7.7%). This relationship with malignancy occurrence in BP was statistically significant for univariate analysis only (OR = 2.05, 95% CI = 1.03–4.60, p = 0.03). The BP patients and controls had a history of similar types of cancers, and the most common ones in BP patients and controls were also the most common in the general population (such as lung, prostate, breast, ovarian, and colon cancers as well as lymphoma or leukemia).

Other comorbidities

Out of all examined comorbidities, at least 1 comorbidity was present in 199/218 (91.3%) of BP patients and in 132/168 (78.6%) of controls. In BP patients and controls, arterial hypertension was the most frequent comorbidity (in 76.1% and 59.2% subjects, respectively). Arterial hypertension was independently associated with BP in multivariate regression analysis (OR = 2.17, 95% CI = 1.35–3.49, p = 0.001). No association with diabetes mellitus among patients and controls was found. Chronic various drug intake was noted in 96% of BP patients. The most frequently prescribed drugs in BP were ACE-inhibitors, furosemide, calcium channel blockers, aspirin, proton pump inhibitors, and statins.

Discussion

Association with neurological diseases

Our case-control study has shown a remarkably higher incidence of NDs in BP patients (33.5% vs 11.3% in controls). This is consistent with other studies published so far, where ND rates ranged from 23% to 73.8% in BP patients and from 4% to 24.2% in controls.[2,5,7–14,23,26,27] Additionally, our results have indicated that Polish BP patients were approx. 4 times more likely to suffer from any type of ND as compared to other individuals. This high value is also comparable with the results of a recently-published first meta-analysis covering 14 case-control or population-based studies from Europe (Czech Republic, France, Italy, Portugal, Denmark, Spain, and the UK), the US and Asia (Taiwan and Malaysia).[14] In this meta-analysis, BP patients have been estimated to be 5 times more likely to have ND than the general population.[14]

Moreover, similarly to previously published studies, we were not able to demonstrate that all NDs assessed separately had a higher association with BP. The reasons for these discrepancies between various studies may be explained by the different age of BP patients, relatively small patient groups in some evaluations, different selection of control groups, environmental factors, and finally, low morbidity for certain NDs such as epilepsy or multiple sclerosis. Also, the retrospective nature of the studies discussed may have influenced these differences.

In fact, we have shown that dementia was the only ND significantly associated with BP as demonstrated using multivariate regression analysis. Occurring in 20.6%, dementia in our BP patients remained in the middle range of percentages in comparison to previously published studies, where the frequency oscillated from 5.3% to 42.7%.[1,2,5,6,8–13,26,27] It is also important to note that, based on data from PubMed, dementia was independently associated with BP in all of the 13 case-control or population-based studies evaluating the relationship of this entity among BP patients confirmed by multivariate regression analysis, although the incidence of dementia varied considerably and ranged from 2.5 to 12.9 times more than in the general population.[1,2,5,6,9–12,14] Our BP patients faced a 7.86-fold increased risk of dementia, similarly to English patients with BP.[5]

Surprisingly, we observed a much older age of BP patients with dementia compared to BP patients without this condition (a difference of 8 years, p = 0.0015). The same was true when compared to the control group (a difference of 8 years, p = 0.07). In the literature, the data on BP patients' age with dementia is very limited. Only Langan et al., in a large group of 868 patients and 3,453 controls, noted a higher proportion of elderly BP patients with dementia compared to healthy controls with dementia.[1]

Interestingly, similarly to dementia, our BP patients with any type of ND were also older than BP patients without ND (a difference of 5 years). In the literature, several studies have evaluated the mean age of BP patients with any type of ND, showing that French, German and Iranian populations of BP patients with ND were much older than those without ND (a difference of 4, 7 and 17 years, respectively).[7,11,28] The significance of the abovementioned findings is difficult to explain, especially as one could expect the opposite results. It seems that these unexpected results need confirmation in subsequent observations.

In our BP patients, the profile of other NDs was 12.8% for stroke, 5% for Parkinson's disease, less than 1% for epilepsy, and less than 1% for multiple sclerosis, being the closest to the French group of BP patients.[8] According to the literature, the prevalence of stroke in BP is estimated at between 7.7% to 44.4%, Parkinson's disease is reported between 2.3% and 17.9% of BP patients, the frequency of epilepsy varies from 2% to 11.1% and the frequency of multiple sclerosis is estimated at between 0% and 5%.[1,2,5,6,8–11,13–15,26–28]

We identified a relationship between BP and stroke, but the association was lost in the multivariate regression analysis. In fact, 12 case-control or population-based studies out of 15 which evaluated the prevalence of stoke in BP using multivariate regression analysis showed no significant association of this disorder among BP patients.[1,2,5,6,8–11,13–15,26,27]

Our study did not show greater incidences of multiple sclerosis, Parkinson's disease or epilepsy among BP patients either. Although the relationship between multiple sclerosis and BP is the strongest among all the NDs, probably due to the autoimmune nature of both disorders, studies of American and Iranian populations of BP patients did not

show an increased risk of multiple sclerosis, similarly to our study.[2,11] Congruous observations for Parkinson's disease or epilepsy and BP can be noted too. Until now, in 4 case-control studies, an increased relationship with Parkinson's disease was revealed[1,2,6,10,12] but the results of 5 others did not confirm this observation with multivariate regression analysis.[2,5,10,13] Likewise, several studies have investigated the prevalence of epilepsy in BP and in 3 of them a positive association was observed,[1,10,15] while the English, Malaysian and Iranian studies did not note such an association at all.[5,11,13]

The interaction between NDs and BP might play a crucial role in the explanation of the pathological mechanisms in BP. In fact, both cutaneous BP antigens BPA2 and BPA1 (neuronal isoform) are found in the central nervous system. It has been suggested that alterations of the blood–brain barrier in the course of NDs may expose the neuronal BP antigens leading to an autoimmune response which results in the development of BP. A recent study by Messingham et al. proved that patients with various forms of dementia and Parkinson's disease even without BP had BPA2 antibodies detected in 23% and 37% of cases, which may confirm this hypothesis.[29] Such patients have been suggested to represent a pre-disease state in which, firstly, neuronal immunoreactivity against BP180 is manifested, and later, as a result of some additional triggers, cutaneous autoimmunity is developed.[30]

Association with malignancies

In contrast to NDs, the relationship between BP and malignancies has been under debate for many years. The results of our study showed a positive association between BP and malignancy occurrence, but various case-control studies have revealed the opposite results so far. Based on data from studies published in PubMed, the incidence of malignancies among BP patients ranged from 5.8% to even 21.3%. However, in some of these studies, no association was observed as compared to the control group. For example, a large English epidemiological study which included many cases of BP patients did not detect a higher risk of cancer in these patients in contrast to the general population.[16] In another study carried out by Lindelof et al. in Swedish BP patients, no association between BP and malignancies was found.[31] Unlike the abovementioned studies, some others have suggested an increased frequency of malignancies in BP patients.[17,18,19,23] Studying a German population of BP patients (1,743 patients), Schulze et al. found that BP patients face a 2.5-fold higher risk of different hematological malignancies, with a percentage of 6.7% in BP patients.[19] Moreover, Ogawa et al. investigated a large Japanese population of BP patients (1,113 patients) and found malignant diseases in 5.8% of patients compared with 0.61% among controls.[18] In addition, a case-control study of the Danish population disclosed a slightly higher incidence of tumors in BP patients (14%), but no statistical analysis was conducted to clarify these findings.[23] There are also numerous single case reports that have determined the co-existence of certain carcinomas. These cases were analyzed jointly by Balestri et al., showing that cancers of the prostate, breast, stomach and colon, as well as lymphoma and leukemia were observed the most often in BP patients.[32]

Some authors have emphasized that the coexistence of BP and malignancies should not be found surprising as they result from the high rate of malignancies in this elderly patient population. The open question is if there is a common pathophysiological pathway of BP and malignancies. So far, several hypotheses have been proposed to explain this concomitance. The first and main theory suggests that antibodies against tumor-specific antigens may cross-react with the BMZ. Another one indicates that a tumor could secrete a hormone-like substance destroying BMZ, which causes the production of anti-BP antibodies. Another hypothesis considers the role of an external factor, e.g., a virus, which could be tumorigenic and lead to BMZ destruction at the same time.[32]

Association with cardiovascular diseases

Finally, our data demonstrated the significant association between BP and arterial hypertension revealed by multivariate regression analysis. The prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing.[33] In both groups studied, arterial hypertension was the most common comorbidity, however it seems to be more frequent in BP patients. Our results were consistent with recently published studies carried out by Kremer et al., who found that arterial hypertension was the most frequent comorbidity in BP (in 64% of patients studied, $p = 0.04$).[21] In studies by Kwan et al. and Cai et al., arterial hypertension was also the most frequent out of all comorbidities (in 62.8% and 59.3%, respectively).[13,20] In another study concerning BP patients, multi-morbidity was observed in 84% with the highest percentage for arterial hypertension.[22] On the other hand, Jedlickova et al. did not find differences in cardiovascular disease incidences among patients with BP and controls.[7]

Nevertheless, a certain role in the pathogenesis of BP is attributed to drug consumption, especially agents used to treat hypertension. We suppose that positive association with arterial hypertension occurrence in our patients might also be related to antihypertensive drugs, which in some cases could certainly contribute to inducing or exacerbating BP.[23] Similarly, in our BP patients with arterial hypertension, the intake of at least 1 antihypertensive drug was noted; therefore, the potential influence of prescribed treatment on BP course cannot be excluded either.

Limitations

Our single-center study includes some limitations. The first is the retrospective nature of our evaluation.

Moreover, the hospitalized patients with other dermatological conditions serving as controls in this study might contribute to a certain selection bias.

Conclusions

Our study on a relatively large group of BP patients demonstrated a significantly higher prevalence of various NDs, especially dementia. Surprisingly, the BP patients with any NDs, presented were older than the BP subjects without these disorders. Among other common comorbidities, arterial hypertension and other malignancies typical for the general population were the ones most associated with BP occurrence. For appropriate medical care, patients with BP need accurate screening, especially for dementia and any neurological abnormalities. Interdisciplinary management of BP patients including dermatologists, neurologists, cardiologists, and general practitioners is strongly required.

References

1. 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(3):631–636.
2. Brick KE, Weaver CH, Savica R, et al. A population-based study of the association between bullous pemphigoid and neurologic disorders. *J Am Acad Dermatol.* 2014;71(6):1191–1197.
3. Serwin AB, Musialkowska E, Piascik M. Incidence and mortality of bullous pemphigoid in north-east Poland (Podlaskie Province), 1999–2012: A retrospective bicentric cohort study. *Int J Dermatol.* 2014;53(10):e432–437.
4. Kalinska-Bienias A, Lukowska-Smorawska K, Jagielski P, Kowalewski C, Wozniak K. Mortality in bullous pemphigoid and prognostic factors in 1st and 3rd year of follow-up in specialized centre in Poland. *Arch Dermatol Res.* 2017;309(9):709–719.
5. Taghipour K, Chi CC, Vincent A, Groves RW, Venning V, Wojnarowska F. The association of bullous pemphigoid with cerebrovascular disease and dementia: A case-control study. *Arch Dermatol.* 2010;146(11):1251–1254.
6. Bastuji-Garin S, Joly P, Lemordant P, et al; French Study Group for Bullous Diseases. Risk factors for bullous pemphigoid in the elderly: A prospective case-control study. *J Invest Dermatol.* 2011;131(3):637–643.
7. Jedlickova H, Hlubinka M, Pavlik T, Semradova V, Budinska E, Vlasin Z. Bullous pemphigoid and internal diseases: A case-control study. *Eur J Dermatol.* 2010;20(1):96–101.
8. Cordel N, Chosidow O, Hellot MF, et al; French Study Group for Bullous Diseases. Neurological disorders in patients with bullous pemphigoid. *Dermatology.* 2007;215(3):187–191.
9. Yu Phuan CZ, Yew YW, Tey HL. Bullous pemphigoid and antecedent neurological diseases: An association with dementia. *Indian J Dermatol Venereol Leprol.* 2017;83(4):457–461.
10. Chen YJ, Wu CY, Lin MW, et al. Comorbidity profiles among patients with bullous pemphigoid: A nationwide population-based study. *Br J Dermatol.* 2011;165(3):593–599.
11. Daneshpazhooh M, Khorassani J, Balighi K, et al. Neurological diseases and bullous pemphigoid: A case-control study in Iranian patients. *Indian J Dermatol Venereol Leprol.* 2017;83(2):195–199.
12. Casas-de-la-Asuncion E, Ruano-Ruiz J, Rodriguez-Martin AM, Rodriguez-Martin AM, Velez Garcia-Nieto A, Moreno-Gimenez JC. Association between bullous pemphigoid and neurologic diseases: A case-control study. *Actas Dermosifiliogr.* 2014;105(9):860–865.
13. 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(2):81–85.
14. Lai YC, Yew YW, Lambert WC. Bullous pemphigoid and its association with neurological diseases: A systematic review and meta-analysis. *J Eur Acad Dermatol Venereol.* 2016;30(12):2007–2015.
15. Forsti AK, Jokelainen J, Ansakorpi H, et al. Psychiatric and neurological disorders are associated with bullous pemphigoid – a nationwide Finnish Care Register study. *Sci Rep.* 2016;6:37125.
16. Ong E, Goldacre R, Hoang U, Sinclair R, Goldacre M. Associations between bullous pemphigoid and primary malignant cancers: An English national record linkage study, 1999–2011. *Arch Dermatol Res.* 2014;306(1):75–80.
17. Iwashita K, Matsuyama T, Akasaka E, et al. The incidence of internal malignancies in autoimmune bullous diseases. *Tokai J Exp Clin Med.* 2007;32(1):42–47.
18. 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(2):136–141.
19. Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. *J Invest Dermatol.* 2015;135(5):1445–1447.
20. Cai SC, Allen JC, Lim YL, Tan SH, Tang MB. Association of bullous pemphigoid and malignant neoplasms. *JAMA Dermatol.* 2015;151(6):665–667.
21. Kremer N, Zeeli T, Sprecher E, Geller S. Failure of initial disease control in bullous pemphigoid: A retrospective study of hospitalized patients in a single tertiary center. *Int J Dermatol.* 2017;56(10):1010–1016.
22. Sim B, Fook-Chong S, Phoon YW, et al. Multimorbidity in bullous pemphigoid: A case-control analysis of bullous pemphigoid patients with age- and gender-matched controls. *J Eur Acad Dermatol Venereol.* 2017;31(10):1709–1714. doi:10.1111/jdv.14312
23. Kibsgaard L, Bay B, Deleuran M, Vestergaard C. 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(3):307–311.
24. Chuang TY, Korkij W, Soltani K, Clayman J, Cook J. Increased frequency of diabetes mellitus in patients with bullous pemphigoid: A case-control study. *J Am Acad Dermatol.* 1984;11(6):1099–1102.
25. Li J, Zuo YG, Zheng HY, Qiu-Ning S. Association between bullous pemphigoid and internal diseases. *J Dtsch Dermatol Ges.* 2013;11(3):263–264.
26. Pietkiewicz P, Gornowicz-Porowska J, Bowszyc-Dmochowska M, Bartkiewicz P, Dmochowski M. Bullous pemphigoid and neurodegenerative diseases: A study in a setting of a Central European university dermatology department. *Aging Clin Exp Res.* 2016;28(4):659–663.
27. Tarazona MJ, Mota AN, Gripp AC, Unterstell N, Bressan AL. Bullous pemphigoid and neurological disease: Statistics from a dermatology service. *An Bras Dermatol.* 2015;90(2):280–282.
28. Gambichler T, Segert H, Hoxtermann S, Schmitz L, Altmeyer P, Teegen B. Neurological disorders in patients with bullous pemphigoid: Clinical and experimental investigations. *J Eur Acad Dermatol Venereol* 2015;29(9):1758–1762.
29. Messingham KA, Aust S, Helfenberger J, et al. Autoantibodies to collagen XVII are present in Parkinson's disease and localize to tyrosine-hydroxylase positive neurons. *J Invest Dermatol.* 2016;136(3):721–723.
30. Kokkonen N, Herukka S-K, Huilaja L, et al. Increased levels of the bullous pemphigoid BP180 autoantibody are associated with more severe dementia in Alzheimer's disease. *J Invest Dermatol.* 2017;137(1):71–76.
31. Lindelof B, Islam N, Eklund G, Arfors L. Pemphigoid and cancer. *Arch Dermatol.* 1990;126(1):66–68.
32. Balestri R, Magnano M, La Placa M, et al. Malignancies in bullous pemphigoid: A controversial association. *J Dermatol.* 2016;43(2):125–133.
33. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2013;34(28):2159–2219.