Bullous pemphigoid – what makes the blister?

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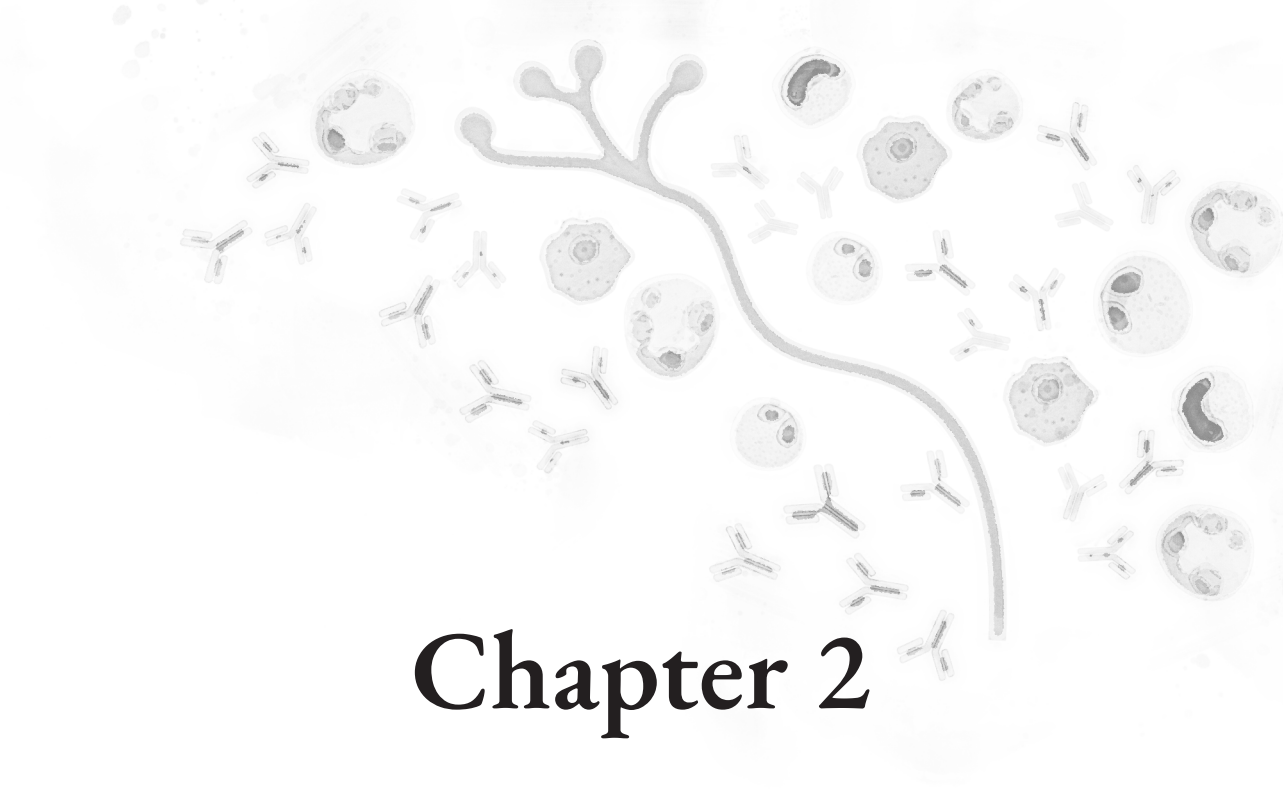
DOI:
10.33612/diss.1111217604



Chapter 2

Neurological disorders are associated with bullous pemphigoid

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Published in: *J Eur Acad Dermatol Venereol*. 2019 May;33(5):925-929

Abstract

Background Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering disease with an increased incidence particularly among the elderly. Several studies have recently reported an association between BP and neurological disorders.

Objective To evaluate the association between BP and neurological disorders in a single centre in Germany.

Methods We retrospectively assessed 183 patients with BP (diagnosed between 2011 and 2015) and 348 age- and sex-matched controls for neurological disorders. The latter were confirmed either by a neurologist or psychiatrist.

Results Overall, there was a highly statistically significant association between BP and neurological disorders ($P < 0.0001$). These included dementia ($P < 0.0001$), Parkinson`s disease ($P = 0.0434$), stroke ($P = 0.0015$) and other neurological disorders but not Alzheimer's diseases, which was more common among patients in the control group.

Conclusion Our cohort of bullous pemphigoid and neurological disorders demonstrates a significant association between bullous pemphigoid and neurological disorders, including dementia, Parkinson's disease and stroke. These observations support the need for future studies in order to elucidate the immunological mechanisms responsible for these comorbidities.

Conflicts of interest

The authors declare no conflicts of interest.

Funding sources

This work was funded by a DFG grant to Ulrike Raap RA 1026/3-1.

Introduction

Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering disease[1] affecting the elderly[2]. Clinically, the early phases of BP often show flares, and sometimes additionally heals with strong pruritus, while flares associated with the late phase are also accompanied by tense blisters.[1] The disease is characterized by the production of IgG autoantibodies to BP180 (also called BPAG2 or type XVII collagen) and BP230 (BPAG1-e), two major molecular components of the hemidesmosome in the basement membrane[3,4]. These autoantibodies have been demonstrated to be directly pathogenic by triggering an inflammatory cascade that leads to tissue damage and, ultimately, to subepidermal blister formation[5]. The main autoantigen, BP180, is a transmembrane hemidesmosome protein which links basal keratinocytes to the underlying dermis[6]. It is expressed in the skin and in various other tissues, but there is contradictory evidence regarding its expression in the central nervous system. Whereas BP180 was reported to be expressed in neurons of the cerebral cortex, hippocampus and amygdala of the human brain,[7,8] Barric *et al.,*[9] in contrast, failed to observe BP180 in the hippocampus. The absence of BP180 expression is further supported by data from The Human Protein Atlas or other public databases as previously reviewed[10].

The other major autoantigen of BP, BP230 is an intracellular component of hemidesmosomes and is the epithelial isoform of Dystosin. Its variants, BPAg1a1 and BPAg1a2, are expressed in the central and peripheral nervous system[10]. BP is also characterized by a substantial increase in numbers of activated eosinophils both in the blood and the skin (including blister fluids) of BP patients[11,12].

There is growing evidence to suggest an association between BP and a range of neurological disorders including dementia, cerebral stroke, Parkinson's disease, cerebrovascular disease, multiple sclerosis, epilepsy and polyneuropathies[13–22]. While the immunological mechanisms have not been fully elucidated, the association between BP and neurological disorders may be due to immune responses arising from cross-reactivities of skin autoantibodies with BP antigens or their isoforms that are known to be expressed in brain and neuronal tissue[8,10,14,23].

In our study, we aimed to analyse the clinical characteristics of patients with BP and to assess the relationship between BP and neurological disorders. We therefore evaluated the prevalence and types of neurological disorders in a series of 183 consecutive BP patients in comparison to 348 age- and sex-matched controls.

Materials and methods

This was a retrospective case–control study involving 183 patients (125 women and 58 men, with a mean age of 80 years) diagnosed with BP, based on the international coding of disease (ICD), seen in our clinic in Germany between 2011 and 2015. The diagnosis of BP was confirmed histopathologically as well as by direct and indirect immunofluorescence. Relevant patient data were collected from the medical records, and the BP patients were divided into two groups: either those with neurological disorders or those without. Neurological disorders were confirmed either by a neurologist or a psychiatrist. All cases (BP patients and also control patients) underwent neurological evaluation.

BP patients were compared with 348 age- and sex-matched controls. Control patients were randomly selected from our clinical database of cases between 2011 and 2015, including patients with inflammatory dermatoses (matched according to age and sex). Since BP is an inflammatory skin disease our control group consisted of patients with non-BP-related inflammatory skin diseases in order to avoid the bias of missing inflammation. These included patients with inflammatory dermatoses, such as erysipelas, psoriasis vulgaris, prurigo nodularis, other forms of prurigo, nummular dermatitis, generalized skin eruption due to drugs, ulceration of the lower limb and varices of the lower extremities (with both ulcers and inflammation). Neurological disorders were confirmed either by a neurologist or a psychiatrist. The composition of the control group is fully described in Table 1.

Statistical analysis was carried out using GraphPad Prism (GraphPad Prism v.7; GraphPad Software, Inc., San Diego, CA, USA). Binary logistic regression was used to calculate the odds ratio (OR) and 95% confidence intervals (95% CI) for neurological disorders and comorbidities. A *P*-value of <0.05 was considered as statistically significant.

Table 1 Composition of different inflammatory dermatoses in the control group

Inflammatory dermatoses	ICD-10	Number of inflammatory dermatoses (n = 348)
Erysipelas	A46	80 (23)
Psoriasis vulgaris	L40.0	72 (21)
Prurigo nodularis	L28.1	17 (5)
Other prurigo	L28.2	57 (16)
Nummular dermatitis	L30.0	39 (11)
Generalized skin eruption due to drugs and medicaments	L27.0	38 (11)
Ulcer of lower limb, not elsewhere classified	L97	12 (3)
Varices of lower extremities with both ulcer and inflammation	I83.2	33 (9)

The mean age of the BP group was 80 ± (SD) 12 years, and in the control group, it was 79.7 ± (SD) 3 years. Neurological disorders included either Parkinson's disease, dementia, stroke, Alzheimer's disease, epilepsy or polyneuropathies. The study group is summarized in Table 2.

108 patients (59%) had a history of at least one neurological disorder at the time of BP diagnosis, without distinction of gender, compared to only 41 patients (12%) in the control group. Overall, neurological disorders were significantly associated with BP ($P < 0.0001$). The calculated odds ratio was 10.8 (Table 2). Immunopathological characteristics, in terms of BP180 and BP230 autoantibody expression by ELISA between BP patients with or without neurological disorders, were not significantly altered (results not shown), in agreement with Taghipour *et al.*[24] Fifty-nine of 183 patients with BP (32%) suffered dementia compared to 16 patients (5%) in the control group, a difference which was highly significant ($P < 0.0001$; see Table 2).

Table 2 Comparison of neurological disorders between patients with BP and control patients

Disease	Number of BP cases % (n = 183)	Number of controls % (n = 348)	Odds ratio (OR)	95% confidence interval (CL)	P-value
Neurological disorders	108 (59)	41 (12)	10.8	6.9–16.7	<0.0001
Dementia	59 (32)	16 (5)	9.9	5.4–17.8	<0.0001
Alzheimer's disease	0	2 (1)	0.3	0.0–7.9	0.5303
Stroke	16 (9)	8 (2)	4.1	1.7–9.7	0.0015
Parkinson's disease	9 (5)	6 (2)	2.9	1.0–8.4	0.0434
Other neurological disorders	24 (13)	9 (2)	5.7	2.6–12.5	<0.0001

Results

A total of 183 patients with BP were compared to 348 age- and sex-matched controls. 125 of 183 BP patients (68%) were women while 58 patients (32%) were men (women: men, 2:1).

In the BP group, 16 patients (9%) suffered from neurological disorders due to stroke and nine patients (5%) from Parkinson's disease compared to eight (2%) and six (2%), respectively, in the control group. Furthermore, there was a statistically significant association between BP and stroke (P = 0.0015) as well as Parkinson's disease (P = 0.0434; see Table 2).

Twenty-four of 183 patients with BP (13%) had other neurological disorders, such as depression or polyneuropathies, compared with nine patients (2%) in the control group, a difference which was also highly statistically significant (P < 0.0001; see Table 2).

In contrast, the incidence of Alzheimer's disease between the BP and the control groups was not statistically different (P = 0.5303; see Table 2).

Discussion

Our results clearly demonstrate that neurological disorders are more common among patients with BP than those with other dermatological disorders. While previous studies have reported an association between BP and neurological disorders, the specific subset of these disorders is different from the current investigation. In part, this may be due to the age of the BP patients, which in recent studies ranged from 64 to 83 years[14–16,18,19,21,25]. We observed that dementia was the most prevalent neurological disorder in patients with BP (32%). This association is in line with Kwan *et al*[20]. who conducted a retrospective case– control study on 43 patients with BP and reported that dementia was the only neurological disorder that had any statistically significant association ($P = 0.002$) with this autoimmune disease. The high number of patients with BP and dementia in our study cannot be merely ascribed to the age of the patients, which was similar for non-BP controls. The incidence of BP increases significantly after the age of 60 years. The prevalence of dementia in Europe is 14.35% for men and 16.39% for women between 80 and 84 years and 6.89% for men and 7.63% for women between 75 and 79 years[26]. Interestingly, the prevalence of dementia in our control group, which was composed of patients with other dermatological disorders, was surprisingly low (5%).

The low prevalence of dementia in our study may, in part, be explained by the retrospective study design and by sampling only from a single centre. Another possibility could be that dementia is a creeping process, and the symptoms vary across types and stages, which makes a diagnosis difficult. Furthermore, medications used for the treatment of inflammatory dermatoses have a neuroprotective effects, such as in erysipelas therapy[27,28]. Inflammatory dermatoses may also have an unknown protective effect regarding dementia, although this has to be resolved in further studies.

It has previously been shown that the incidence of cerebrovascular accident (CVA) and dementia in patients with BP is significantly elevated[18.] Tarazone *et al*[19]. also revealed a significantly greater prevalence of neurological disorders, especially CVA and dementia, in patients with BP. With 9%, stroke was the second most common neurological disorder in patients with BP, with a highly statistically significant association ($p = 0.0015$). This association concurs with the previous study by Teixeira *et al*[25]. who also reported an association between BP and stroke as well as dementia.

In the present study, we observed a statistically significant association between BP and Parkinson's disease ($p = 0.0434$), which affected 5% of BP patients. This is in agreement with a previous report regarding the association of BP with neurological disorders, especially dementia and Parkinson's disease[15]. Försti *et al.* observed

that neurological disorders which cause central nervous system inflammation or degeneration were related to BP and the association was strongest between multiple sclerosis and BP[16]. Indeed, an association between multiple sclerosis and BP has also been observed in several other reports[14,21,22]. Interestingly, other conditions such as dementia, Parkinson's disease, epilepsy, stroke, schizophrenia, schizotypal and delusional disorders, as well as personality disorders also revealed a statistically significant association with BP[17].

In contrast to other neurological conditions, Alzheimer's disease was not seen to be significantly associated with BP in the present study. However, Kibsgaard *et al.*[21] reported, that Danish patients with BP expressed an increased prevalence of Alzheimer's disease, as well as multiple sclerosis and stroke, in a population-based cohort study. The lack of clear association with Alzheimer's disease and BP in our study may, in part, be explained by the retrospective study design and by sampling only from a single centre. Further studies to support a clear association between Alzheimer's disease and BP are therefore warranted.

Generally, an existing neurological disorder appears to increase the risk for subsequent BP[14– 16,21,29,30]. However, an increased risk for developing some neurological disorders following BP diagnosis, such as multiple sclerosis, strokes and epilepsy has also been reported[15,16,21].

Based on the association of different neurological disorders with BP and the expression of BP autoantigens in the central nervous system, it has been suggested that neuroinflammation could lead to a cross-reactive immune response between neural and skin antigens[8,10,14]. Indeed, Foureur *et al.*[31] reported the presence of autoantibodies against BP180-NC16A in subjects with dementia, despite a lack of signs of BP. They also revealed that the presence of anti-PBAg2 antibodies was associated with the diagnosis of dementia ($P = 0.04$)[31]. In contrast, Messingham *et al.*[32] showed in a recent study that only one in 26 patients with various dementia types expressed autoantibodies against BP180-NC16A. However, sera from Parkinson's disease patients exhibited reactivity to sec180 in immunoblot assays and autoantibodies colocalized with tyrosine hydroxylase-positive (TH^+) dopaminergic neurons in the rat substantia nigra[32].

Increased levels of BP180 autoantibodies were recently reported to be associated with severe dementia in Alzheimer's disease[23]. Here, autoantibodies in sera from patients with Alzheimer's disease ($n = 115$) recognized the full-length BP180 autoantigen in immunoblots and bound to the NC16A domain in ELISA assays. However, none of the sera from Alzheimer's disease patients that recognized full-length human BP180 by immunoblot reacted with the cutaneous basement membrane using indirect immunofluorescence analysis. Furthermore, a retrospective evaluation of

the hospital reports of patients with Alzheimer's disease revealed neither BP diagnosis nor BP-like symptoms[23]. Despite this, Chen and colleagues demonstrated that sera of elderly BP patients with associated neurological disorders recognize BP antigens in the human epidermis and brain, where BPAG1 could act as a shared antigen[33].

The reported differences in the proportions of patients with neurological disorders displaying autoantibodies to BP antigens may be due to differences in either the methods or study populations. It also remains obscure what triggers autoimmunization against the BP180 and BP230 autoantigens. The proposed cross-reactive immune response between neural and cutaneous antigens is supported by the strong association between BP and several neurological disorders, but this cannot explain the failure of immune tolerance against BP180 in neurologically healthy BP patients. Further studies are therefore required to clarify the molecular mechanisms behind this association.

Since the mechanisms underlying this association have not yet been elucidated, it could be argued that either statistical distortions or non-biological effects are responsible for these observations. However, given the relatively large number of previously published reports demonstrating a robust statistical link between neurological diseases and BP statistical distortion issues are unlikely to have affected our observations.

In conclusion, the results obtained in this study clearly indicate an association between BP and neurological disorders, including dementia, Parkinson's disease and stroke in German patients, supporting similar associations in previous studies. However, the immunological mechanisms for these comorbidities have yet to be fully resolved.

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