Neurological and psychiatric associations in bullous pemphigoid – more than skin deep?

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Abstract

In elderly patients, bullous pemphigoid (BP) is associated with several comorbidities; the strongest association occurs between BP and neurological diseases. Different types of dementia, Parkinson's disease, cerebrovascular disorders and epilepsy all have a significant association with BP but patients with multiple sclerosis have the highest risk of BP. An existing neurological disorder appears to increase the risk for subsequent BP, but an increased risk for developing some neurological diseases has also been reported following BP diagnosis. BP seems to be associated with several psychiatric diseases such as schizophrenia, uni- and bipolar disorder, schizotypal and delusional disorders, and personality disorders, but the risk ratios are usually lower than with neurological diseases. In addition to the skin, the BP autoantigens BP180 and BP230 are expressed in the central nervous system. This finding together with the strong epidemiological association between neurological disorders and BP has led to an assumption that neurodegeneration or neuroinflammation could lead to a cross-reactive immunoresponse between neural and cutaneous antigens and the failure of self-tolerance. A subpopulation of patients with Alzheimer's disease or Parkinson's disease have circulating IgG autoantibodies against BP180, but currently their significance for the development of BP is unclear, since these anti-neural BP180 antibodies neither bind to the cutaneous basement membrane nor cause BP like symptoms. Further studies analyzing large and well-characterized populations of neurological and psychiatric patients are required to understand better the role of autoimmunization against neural BP autoantigens in the pathogenesis of BP.

KEY WORDS: BP180, collagen XVII, autoimmune disease, dementia, multiple sclerosis

1 INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering skin disease, which is most commonly found in elderly people, and has a growing incidence within this age bracket.[1-5] Its incidence has recently been calculated as 59/ million/year in Germany in 2014 6. The importance of autoantibodies against BP180 in the pathogenesis of BP is undisputable, but it is largely unknown what initiates the loss of immunological tolerance against this basement membrane component in the aging skin. BP onset is usually seen in patients who are in their late 70s [4,5,7] and generally speaking, BP patients have many comorbidities due to advanced age. The most frequently reported conditions are neurological diseases, cardiovascular diseases and diabetes [5,7-12]. An association between BP and malignancies is suspected [13], although no such connection has been confirmed, despite several studies [14-17]. Recently, however, a clear association of BP with hematological malignancies has been established by a study of about 1,700 BP patients based on data from a health insurance company [18]. Of all BP's comorbidities, the strongest association is between BP and neurological diseases [19-21]. This finding in conjunction with the expression of BP autoantigens in the central nervous system (CNS) has led to a suggestion that neurodegeneration or neuroinflammation could trigger the initiation of autoimmunization [20,22-24].

The association of BP with neurological disorders has been recently analyzed in systematic reviews [25,26]. The aim of the present review is to assess the epidemiological data concerning the link between BP and neurological and psychiatric comorbidities and, especially, the putative molecular mechanisms behind the association.

2 BP AND NEUROLOGICAL DISEASES

The association between BP and neurological disorders was first suggested in case reports from the 1980s which described BP patients with preceding multiple sclerosis (MS) [27,28]. Today the link has been shown by several case-control studies, case series and large population based studies (Table 1). A recent meta-analysis also confirmed a significant association between BP and several neurological diseases [26].

Among patients with neurological disorders, those with MS are between 5.9 and 15.4 times more likely to develop BP than control populations [12,20,29-31]. Since both MS and BP are autoimmune diseases, this association is not very surprising, but it is remarkable that according to MS cohort studies, BP is the most common other autoimmune disease in MS patients [29,30]. Of note, BP occurs on average 12 years earlier in MS patients than in BP patients in general [31].

Alzheimer's disease, frontotemporal lobar dementia and Parkinson's disease are the most common neurodegenerative disorders; all exhibit some sort of immunological association [32,33]. Several studies have established an association between BP and dementia, but in most, dementia subtypes are not specified [19-21,34-37]. In these studies BP in patients with dementia had an adjusted risk ratio of between 2.2 and 10.1. A recent nationwide Finnish study revealed that BP is associated with all specific dementia categories: compared with non-dementia controls the risk of developing BP is elevated 2.6-fold in patients with Alzheimer's disease, 3.6-fold in those with vascular dementia and 3.8-fold in those with other/indeterminate dementia [31].

BP also has a significant association with Parkinson's disease, and the risk ratio of BP in patients with Parkinson's disease has been reported as between 2.2 and 9.0 [12,19-21,31,34-37].

As expected, elderly BP patients suffer from cerebrovascular disorders. Several studies have demonstrated an association between BP and stroke, the adjusted risk varying between 1.8 and 6.0 [12,19-21,31,34-39]. Previous studies have examined the association between BP and stroke, but with 'stroke' being an unspecific term covering an array of cerebrovascular disorders. A recent nationwide study of more than 4.500 BP patients in Finland divided cerebrovascular disorders into subarachnoid hemorrhages, intracerebral hemorrhages, and cerebral infarctions. The study found that each condition, despite having a different pathophysiology from the others, carried an approximately 2-fold elevated risk for subsequent BP compared with controls [31].

An association between BP and epilepsy has also been described: Patients with BP have a reported risk ratio of epilepsy between 1.7 and 7.8 [20,31,34]. Of note, a recent meta-analysis concluded that there is high heterogeneity between the studies which have analyzed this association [26]. Perhaps this heterogeneity reflects the fact that epilepsies are a diverse group of disorders, with several underlying pathomechanisms, such as genetic factors, neuroinflammatory and cerebrovascular disorders, traumas and tumors [40].

In general, an existing neurological disorder appears to increase the risk for subsequent BP [12,20,31,36], but conversely, an increased risk for developing some neurological diseases following BP diagnosis, such as MS, strokes, epilepsy, viral meningitis or viral encephalitis, has also been reported [12,29-31,36,38].

It has been suggested that medications used to treat neurological diseases may increase BP risk. Based on current data it is not possible to differentiate whether the elevated risk of BP is driven by the neurological disorder itself or its treatment [19]. Polypharmacy is common among elderly BP patients, and a recent study of 198 BP patients found that about half regularly used more than six concomitant

medications [41]. So far the use of loop diuretics, spironolactone, and neuroleptics has been reported to be associated with BP [19,42]. Recently, increasing numbers of case reports and data from a recent French pharmacovigilance register have linked BP with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors ("gliptins"), which are nowadays widely used for the treatment of diabetes [43-46]. DDP-4 inhibitors are thought to promote eosinophil activation and have also been linked to noninflammatory BP, in which autoantibodies target regions of BP180 other than the immunodominant NC16A domain [43,45]. Further studies characterizing the mechanism of drug-related BP are essential and epidemiological studies with large enough sample sizes are required to detect the true associations between BP and drug intake.

3 BP AUTOANTIGENS BP180 AND BP230

The main BP autoantigen is BP180 (also known as collagen XVII or BPAg2), which is a transmembrane hemidesmosomal component located in the cutaneous basement membrane [47-49]. BP180 is composed of three collagen α1 chains, each of which comprises a globular intracellular N-terminal domain, a short transmembrane stretch, and a large extracellular C-terminal domain, with 15 collagen repeats separated by 16 non-collagenous (NC) subdomains. Each chain is about 1500 amino acids long and the extracellular domain spans the lamina lucida and inserts into the lamina densa before kinking back to the lamina lucida [48,50]. BP180 is also expressed in various other tissues including the brain [22,51-53]. Particularly strong BP180 expression has been detected in post mortem samples of human brain pyramidal cells from the hippocampus and the ganglionic layer of the cortex, regions that are well-recognized predilection areas for Alzheimer's disease-related lesions [22,51,52]. In the brain, BP180 is expressed in neurons [51], but the exact subcellular localization and the function of neural BP180 is not known. The other BP autoantigen, BP230, is the epithelial isoform of dystonin,

and its variants BPAg1a1 and BPAg1a2 are expressed in both the central and the peripheral nervous systems [23,54]. Like other plakins, BP230 contains a globular N-terminal domain, a coiled-coil rod domain and a globular intermediate filament binding (C-terminal) domain. The N-terminus and the first spectrin repeat are followed by the plakin domain, which is composed of several spectrin repeats and an SH3 domain inserted into the 5th spectrin repeat [23,50]. Both BP180 and BP230 are associated with genetic diseases as well as with autoimmune blistering skin diseases: Mutations in the gene coding for BP180 (*COL17A1*) lead to skin blistering in human junctional epidermolysis bullosa [48] whereas mutations in the dystonin gene (*DST*) cause two distinct disorders: epidermolysis bullosa simplex and type VI hereditary sensory and autonomic neuropathy [23].

4 BP AUTOANTIBODIES ARE FOUND IN PATIENTS WITH NEUROLOGICAL DISEASES

Based on the epidemiological association of several neurological diseases with BP and the CNS expression of BP autoantigens it has been hypothesized that neuroinflammation or neurodegeneration could lead to a cross-reactive immunoresponse between neural and cutaneous antigens [20,22-24]. This hypothesis is supported by epidemiological data, which convincingly demonstrate that BP is most strongly associated with neurological diseases involving inflammatory or degenerative alterations in the CNS, such as MS, Alzheimer's disease and Parkinson's disease[32].

An autoimmune response against the neural isoform of BP230 in the brain was initially suggested to explain the association between BP and neurological disorders [20,22,23]. Antibodies against various domains of BP230 have been detected in cerebrospinal fluid (CSF) samples obtained from patients

with MS and some other inflammatory neurological disorders, but since they were also present in the CSF of otherwise healthy control patients, these antibodies were not considered to be disease-specific [23,55]. Several attempts to demonstrate a cross-reactive immune reaction between the neural and cutaneous variants have failed [23,56,57] and therefore the significance of BP230 in the development of BP in patients with neurological disorders is currently unclear.

The studies which have analyzed the presence of circulating BP autoantibodies in neurological patients are summarized in Table 2. A French study was the first to demonstrate that circulating IgG autoantibodies targeting the immunodominant NC16A epitope of BP180 are found in patients with dementia [58]. That study found BP180 autoantibodies in five/69 subjects (7%) with dementia (Mini-Mental State Examination [MMSE] ≤24), but none of the 69 controls (MMSE >24) (58). In a recent study, six patients of 26 (23%) with various dementia types and nine of 24 patients (38%) with Parkinson's disease had antibodies against the intra- or extracellular domain of BP180[53]. Thereafter, another study showed that circulating the NC16A-BP180 IgG autoantibodies were found in 20/115 (17%) of Alzheimers patients whereas only one of the 40 neurologically healthy controls (3%) had positive results[57]. In this study, the presence of anti-BP180 autoantibodies had a significant association with cognitive decline: the lower the MMSE score, the higher the value of the BP180 ELISA [57]. In contrast, a study by Recke and co-workers[56] failed to detect significantly higher levels of autoantibodies against BP180 and BP230 in sera of patients with Parkinson's disease (n=125) and MS (n=50) compared with sex- and aged matched controls. Of note, the mean age of patients with Parkinson's disease was 63 years and that of MS patients only 33 years. Therefore they were younger than BP patients in general, which may explain the negative results.

Based on recent studies that have detected BP180 autoantibodies in the sera of patients with dementia or Parkinson's disease, it seems that cutaneous and neural autoantibodies have differences. Sera from patients with Alzheimer's disease recognized the full-length BP180 in immunoblotting and bound to the NC16A domain in an ELISA assay [57], whereas positive sera from dementia or Parkinson's disease patients reacted with either the entire intra- or extracellular part of BP180, but were mainly negative on a NC16A-BP180 ELISA[53]. However, no anti-neural BP180 antibodies were able to bind to the cutaneous basement membrane in an immunofluorescence analysis and none of the patients had BP like symptoms [53,57]. In a study of samples of human and rat brain samples, BP180 autoantibodies of neurological patients recognized the substantia nigra dopaminergic neurons, which degenerate in Parkinson's disease[53]. More detailed epitope mapping of neural autoantibodies and careful characterization of BP180 in the brain are required to clarify these discrepant results.

Regarding the functional significance of anti-neural BP180 antibodies, it has been suggested that neurological patients with positive BP180 antibodies represent a subgroup of "pre-disease state" BP patients[57]. These patients first have neuronal immunoreactivity against BP180 and later on, due to some additional triggers, some also develop cutaneous autoimmunity. Recently, it has been speculated that HLA-DQB1*03:01, which is overrepresented in BP patients [24,59], may play a role in the anti-BP180 immune response initiated by the process of neurodegeneration or neuroinflammation.

Based on the strong association between MS and BP, it would be surprising if circulating or CSF autoantibodies against BP were not detectable in patients with MS. MS and BP are both prototypic organ-specific autoimmune disease, and T cells, B cells and autoantibodies are important factors in the pathogenesis of both [49,60]. The CSF is usually devoid of immunoglobulins and other plasma proteins, but the CSF of patients with MS typically contains oligoclonal immunoglobulins which are

a biomarker used in the diagnosis of MS and are associated with disease progression and axonal loss in progressive variants of MS [61,62]. The evidence for the pathogenic role of BP autoantibodies is clear and strong, whereas the target antigens of MS autoantibodies are multiple and still remain a matter of debate [61-63]. Intermolecular epitope spreading occurs during the progression of both MS and BP and represents a possible mechanism of the generation of shared immune targets of these two autoimmune diseases [63]. Further analyses of patients with different forms and phases of MS and of experimental autoimmune encephalomyelitis (a murine model of MS) [64] are essential to improve our understanding why MS patients have such a high risk to develop BP.

5 BP AND PSYCHIATRIC DISEASES

BP is associated with several psychiatric diseases, although the risk ratios are usually lower than those seen with neurological diseases [7,31] and the results obtained so far are not consistent. In a large Taiwanese population study, Chen and coworkers showed that patients with schizophrenia are more likely than the general population to develop BP [35], and in a French study[19] it was demonstrated that uni- and bipolar disorders were both independent risk factors for BP. On the contrary, no association was seen between BP and depression in a study by Teixeira and coworkers[21]. A Finnish nationwide study revealed an increased risk of BP in patients with psychiatric diseases, particularly in those with schizophrenia (2.6-fold-risk elevation), schizotypal and delusional disorders (2.1-fold risk elevation) and personality disorders (2.2-fold risk elevation)[31]. In the same study bipolar disorder, depression and neurotic disorders were also associated with an increased risk for BP[31]. However, a large USA study of patients who were hospitalized for BP showed that BP is associated with psychoses and depression, but not with schizophrenia or bipolar disorder [7].

Recent research has suggested involvement of immune cells and neuroinflammation in the pathogenesis of mental health disorders, especially bipolar disorder and schizophrenia [65,66]. Thus it is possible that, as with neurological disorders, psychiatric diseases could increase the risk of BP by neuro-cutaneous cross-reactive immunoreaction. However, it is currently unknown whether levels of autoantibodies against BP180 or BP230 are raised in patients with psychiatric diseases.

6 **FUTURE PERSPECTIVES**

The development of autoimmune diseases is generally increased in immune senescence [67]. Although there is strong evidence from clinical studies and several experimental BP mouse models of a pathogenic role of BP180 autoantibodies, it still remains obscure what triggers autoimmunization against BP180 in the elderly population. The proposal of a cross-reactive immunoresponse between neural and cutaneous antigens is supported by the strong association between BP and several neurological diseases as well as preliminary evidence showing that patients with Alzheimer's disease or Parkinson's disease have BP180 autoantibodies. However, only about 40–60% of BP patients have a comorbid neurological disorder [7,31], and a cross-reactive immunoresponse between the CNS and skin does not explain the failure of immunological tolerance against BP180 in neurologically healthy BP patients.

Further studies analyzing the subcellular localization of BP180 in the brain and characterizing biosynthesis, processing and interactions of BP180 in neurons are needed in order to understand the detailed molecular mechanisms leading to the failure of immunological tolerance against BP autoantigens in the human brain. Careful characterization of BP180 knock-out mice [68,69] and detailed

neurological investigation of patients carrying *COL17A1* mutations could perhaps bring us novel information concerning the function of neural BP180. With regard to the presence of BP180 autoantibodies in patients with neurological disorders, it is unknown what the exact epitopes and IgG subtypes of these autoantibodies are. We must also investigate whether BP180 autoantibodies could be detected in CSF samples. An important question to be answered is why the BP180 autoantibodies of neurological patients do not bind to the cutaneous basement membrane. This could be explored, for example, by comparing the immunoreaction in the human brain between specific BP180 antibodies and anti-BP180 positive samples from patients with various neurological diseases as well as by analyzing whether autoantibodies from patients with BP are able to bind to neural tissue. Until now only autoantibodies against BP180 have been detected in patients with neurological disorders, but the current data do not exclude the possibility of the involvement of the neural isoform of BP230 in the pathogenesis of BP. Further studies analyzing large and well-characterized study populations of neurological patients using several antigens and multiple diagnostic methods will reveal if BP230 has a role in the neural autoimmunization.

Finally, the association between BP and neurological and psychiatric disorders also impacts on daily dermatological practice. It is important for dermatologists to identify and take into account co-morbid diseases in BP patients, since they may limit or hamper the use of systemic therapy or increase morbidity and mortality in BP patients. Furthermore, in patients with severe dementia and other advanced neurological diseases, whose ability to communicate is impaired, BP diagnosis can be missed, especially if blisters are not present and BP manifests as pruritus and non-specific skin symptoms.

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Table 1. Association between bullous pemphigoid and neurological and psychiatric diseases

(BP)	Years	Disorders with a statistically significant association with bullous pemphigoid (BP)	Database/ population	First author, year, country
9317	1999-2011	Motor neuron disease	National Health Service Information Center	Ong, 2013, the UK[70]
4524	1987-2013	Multiple sclerosis, dementia, Parkinson's disease, epilepsy, stroke, schizophrenia, schizotypal and delusional disorders, personality disorder	National Finnish Care Register	Försti, 2016, Finland[31]
3485	1997-2008	Stroke, dementia, Parkinson's disease, epilepsy, schizophrenia, psoriasis	National Health Insurance Research Database	Chen, 2011, Taiwan[35]
3281	1977-2015	Multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke	Danish National Patient Registry	Kibsgaard 2017, Denmark[12]
868	1996-2006	Stroke, dementia, Parkinson's disease, multiple sclerosis, epilepsy	National, General practice database	Langan, 2011, the UK[20]
238	1995-2000	Neurological disease (Parkinson's disease or multiple sclerosis)	Hospitals in North-East Italy	Stinco, 2005, Italy[71]
201	2003-2007	Major cognitive impairment, bedridden condition, Parkinson's disease, unipolar or bipolar disorder	11 hospitals	Bastuji-Garin, 2011, France[19]
190	1992-2012	Neurological diseases	1 hospital	Li, 2013, China[72]
160	2006-2011	Stroke, dementia, Parkinson's disease, epilepsy, multiple sclerosis	1 research center	Daneshpazhooh 2017, Iran[73]
90	2004-2008	Cerebrovascular disease, dementia	1 hospital	Taghipour, 2010, the UK[34]
89	1991-2006	Neurological diseases	2 hospitals	Jedlickova, 2010, the Czech Republic [15]
87	1960-2009	Dementia, Parkinson's disease	Olmsted County, Rochester Epidemiology Project	Brick, 2014, the USA[36]
77	1998-2010	Dementia, stroke, bedridden condition	1 hospital	Teixeira, 2014, Portugal[21]
56	2002-2012	Dementia, Parkinson's disease	1 hospital	Casas-de-la-Asunción, 2014, Spain [37]
43	2004-2013	Dementia	1 hospital	Kwan, 2015, Malaysia [39]
30	1999-2000	Neurological diseases	1 hospital	Foureur, 2001, France[74]

Table 2. Analyses of circulating bullous pemphigoid autoantibodies in patients with neurological diseases

Neurological disease	n (patients/ controls)	Average age of patients/ controls (years)	BP180 ELISA Number of positive cases (patients/ controls)	BP230 ELISA Number of positive cases (patients/ controls)	Western blot analysis	Indirect immunofluorescence (IIF) analysis	First author, year
Dementia	69/69	84/84	4/0, p=0.04	nd[1]	All four BP180 ELISA positive samples and one additional dementia samples recognized BP180 and BP230 in human placenta extract.	All dementia and control samples were tested using IIF. Four BP180 ELISA positive samples and one additional dementia samples were positive.	Foureur, 2006[58]
Alzheimer's disease	115/40	72.0/66.8	20/1, p=0.019	14/3, ns[2]	All BP180 ELISA positive patient samples (n=20) recognized the full-length recombinant BP180. BP230 was not tested.	IIF analysis of 18 BP180 ELISA and Western blot positive samples were negative.	Kokkonen, 2017[57]
Dementia	26/23	na[3]	1/0, ns	1/1, ns	Five patient samples recognized intracellular recombinant BP180 and one recombinant extracellular BP180. BP230 was not tested.	IIF analysis of a subgroup of Western blot positive samples (n=4) were negative.	Messingham, 2016[53]
Parkinson's disease	24/23	na[3]	1/0, ns	1/1, ns	Two patient samples recognized intracellular recombinant BP180 and seven extracellular recombinant BP180. BP230 was not tested.	IIF analysis of a subgroup of Western blot positive samples (n=4) were negative.	Messingham, 2016[53]
Parkinson's disease 75/75[4] 50/65[4]	63.1/63.1 63.5/>70	0/2[5] 2/1[5]	1/2[5] 1/6[5]	All the patient and control samples were negative in immunoblotting against cell-derived BP180 and laminin 332.	All dementia (n=125) and control samples (n=140) were tested using indirect immunofluorescence analysis. Two control samples were positive.	Recke, 2016[56]
Multiple sclerosis	50/65	33.0/>70	0/1[5]	0/6[5]	All the patient and control samples were negative in immunoblotting against cell-derived BP180 and laminin 332.	All multiple sclerosis (n=50) and control samples (n=140) were tested using indirect immunofluorescence analysis. Two control samples were positive.	Recke, 2016[56]

[1]nd, not determined

[2]ns, not significant

[3]na, not available

[4]The study population consisted of two separately collected cohorts of patients with Parkinson's disease which were analyzed separately.

[5]Statistical analysis were not performed

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