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Demographics and Autoantibody Profiles of Pemphigoid Patients with Underlying Neurologic Diseases

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Abstract

Bullous pemphigoid (BP) is an autoantibody-mediated blistering disease that is often associated with neurologic disease. BP antibodies target two epidermal adhesion molecules, known as BP180 and BP230. Homologues to these proteins are found in the brain, and it is hypothesized that neurologic disease leads to the production of autoantibodies that can cross react with their cutaneous forms. To better understand the link between BP and neurologic disease, we evaluated primary demographic features (age, sex, race, ethnicity and elapsed time between onset of skin symptoms and BP diagnosis), severity of BP, and IgG and IgE autoantibody levels in BP controls and BP patients with preceding Parkinson's disease (PD), dementia (DEM), and stroke (STR). The main findings of this study are that BP patients with preceding neurologic disease have a shorter elapsed time between onset of skin disease and BP diagnosis and that subjects with preceding PD or DEM, but not STR, are significantly older than BP patients without neurologic disease. However, no significant differences in clinical presentation, BP severity scores or autoantibody (IgG and IgE) responses were observed amongst the groups. These findings suggest that, despite the age difference, the clinical phenotype of BP is not affected by preceding neurologic disease.

Keywords

bullous pemphigoid; autoantibody; Collagen XVII; neurologic disease; dementia

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CONFILICT OF INTEREST

The authors state no conflict of interest.

DATA AVAILABILITY STATEMENT

Primary research data, including de-identified patient demographics and classification, disease severity scores and raw ELISA values, are available free of charge to all researchers wherever possible and with minimal reuse restrictions.

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by autoantibodies targeting epidermal adhesion molecules, BP180 (collagen XVII) and BP230 (Diaz et al., 1990, Stanley et al., 1988). BP primarily affects individuals ≥ 70 years old and disease risk increases with age (Hubner et al., 2016, Langan et al., 2008). Worldwide, there is an increasing incidence of BP that varies by geographic location; reported rates range from 2.4 to 50 cases per million individuals per year (Brick et al., 2014, Hubner et al., 2016, Joly et al., 2012, Langan et al., 2008, Marazza et al., 2009). An association of BP with neurologic disease was first reported in a 1985 case series of three patients with multiple sclerosis (MS) who developed severe, generalized BP (Simjee et al., 1985). Subsequently, several large case-control and population-based studies estimate that individuals with neurologic disease, such as MS, dementia (DEM) and stroke (STR), are 1.8 – 10.7 times more likely to develop BP than the general population (Bastuji-Garin et al., 2011, Chen Y. J. et al., 2011, Cordel et al., 2007, Forsti et al., 2016, Kibsgaard et al., 2017, Langan et al., 2011, Ren et al., 2017, Taghipour et al., 2010, Yu Phuan et al., 2017). Based on these studies, neurologic disease is now recognized as one of the most common BP comorbidities, affecting 30-60% of patients.

The link between neurologic disease and BP suggests a common mechanism of disease susceptibility or pathogenesis. One possibility is that progressive neurodegeneration and inflammation leads to exposure of neuronal isoforms of the BP180 and BP230 proteins, which facilitates cross reactivity to the skin isoforms (Brown et al., 1995, Kunzli et al., 2016, Li et al., 2009, Seppänen, 2013, Seppanen et al., 2006). Evidence in support of this hypothesis is provided by studies demonstrating serum IgG reactivity to the skin isoforms of BP180 and BP230 in patients who have neurologic disease but not BP (Chen J. et al., 2011, Foureur et al., 2006, Kokkonen et al., 2017, Messingham et al., 2016). Similarly, IgG reactivity to 230-kDa protein of human brain extract was detected in serum from BP patients who did not have neurologic disease (Chen J. et al., 2011).

The significance of the BP180- and BP230-specific antibodies in the pathogenesis of neurologic disease, and their role in the eventual development of BP, remains unclear. Serum IgG antibody reactivity to skin antigens is reported only in a subset (20% or less) of patients with neurologic disease (Foureur et al., 2006, Messingham et al., 2016, Recke et al., 2016). Furthermore, IgE antibodies have not been assessed in patients with BP and neurologic disease, despite the critical role of this autoantibody subclass in the pathogenesis of BP (Fairley et al., 2009). To better understand the association between neurologic disease and BP, we examined patient demographics and circulating IgG and IgE autoantibody levels in BP patients with and without neurologic disease and further determined if particular features were associated with preceding neurologic disease.

RESULTS

Of the 112 BP patients initially identified in our database, 35 (31%) were diagnosed with a preexisting neurologic disease; two of these were excluded due to an unspecified neurologic disease that could not be classified. The remaining 110 BP patients were categorized as

follows: 77 BP patients without neurologic disease (BP CONtrol) and 33 with preceding neurologic disease (ND + BP) which could be sub-divided as 11 Parkinson's disease (PD) + BP, 11 dementia (DEM) + BP, and 11 stroke (STR) + BP. Analysis of patient demographics (Table S1) revealed a similar male to female incidence when ND + BP (43% male) and BP CON (45% male) were compared. When broken down by type of neurologic disease, the STR + BP group was also 45% male, while the PD + BP was 90% male, and the DEM + BP was only 27% male, but these differences were not statistically significant using a chi-square test. Additionally, no differences in race or ethnicity were noted among the study groups, which is typical of BP (Table S1).

Although preceding neurologic disease increases individual risk of developing BP (Bastuji-Garin et al., 2011, Chen Y. J. et al., 2011, Ren et al., 2017), it is not established how it impacts the progression to clinical BP. Studies investigating the association of neurologic disease and BP are problematic. The main issue is that it is difficult to estimate the time between the onset of neurologic disease and development of BP since cognitive decline is gradual and, often, self-reported. In this study, this is further complicated because most of the patients were referred by outside physicians specifically for treatment of BP, but their neurologist was off-site. Based on the information available, the time between onset of skin disease and BP diagnosis (days elapsed) and the age of BP onset were evaluated (Figure 1A, B). The days elapsed was calculated based on the date of first skin symptoms, as perceived by the patient. This information was available for 41 BP CON, 10 PD + BP, 8 DEM + BP and 6 STR + BP subjects. Overall, subjects with all types neurologic disease had a significantly ($p<0.0001$) shorter time between symptom onset and definitive diagnosis of BP (Table 1). In addition, subjects with PD had a significantly shorter ($p<0.0001$) interval to diagnosis of BP than subjects with preceding DEM or STR. Interestingly, when the age of subjects at the time of BP diagnosis was compared (Table 1), subjects with preceding PD (82.7 ± 5.6 years) or DEM (82.6 ± 4.9 years) were significantly older than either BP CON (71.6 ± 10.8 years) or STR+ BP (69.6 ± 8.2 years)(p-values range from 0.0030-0.0052). Upon clinical examination, no differences in morphologic presentation of BP, such as localization of lesions, or BPDAI (Murrell et al., 2012) scores were observed with any type preceding neurologic disease (Figure 1C, Table 1).

If preceding neurologic disease facilitates the development of autoantibodies reactive to cutaneous antigens, this could affect the autoantibody response observed in BP. Thus, circulating antibody levels were measured in patient sera by ELISA. Comparison of BP180 and BP230 IgG levels did not uncover any significant differences in the incidence or specificity of the IgG response in BP patients with or without neurologic disease; however, it is of interest that the highest levels of both antibodies were found in the STR + BP sera (Figure 2, Table 2, Table S2). Total IgE and BP antigen specific IgE, which have not been previously described in BP patients with neurologic disease, were also evaluated (Figure 3, Table 3, Table S2). Consistent with previous studies of BP examining IgE in BP (Iwata et al., 2008, Messingham et al., 2009), subjects with pre-existing neurologic disease exhibited robust production of both total and antigen-specific IgE. Although, no significant differences in the incidence or specificity of the IgE response were observed, the IgE antibody profiles did vary amongst the groups. Specifically, the median BP180 IgE concentration was highest

in the BP CON group, while BP230 and total IgE was the highest in STR + BP (Figure 3, Table S2).

A Spearman's correlation matrix was performed to evaluate the relationships between circulating antibodies, symptom duration, age of BP onset and BPDAI score. Subjects with neurologic disease were evaluated as a group and also by their individual diagnoses. The duration of skin symptoms (days elapsed) was not associated with any other measures in the BP CON group, but was correlated ($p=0.036$, $r=0.459$) with total IgE levels in the neurologic disease + BP group. Although the subjects with preceding neurologic disease were significantly older when diagnosed with BP, no correlations with age were observed in this group. However, in the BP CON group, age at BP diagnosis was inversely related ($p=0.0003$, $r = -0.5086$) to BP180 IgG levels.

Studies evaluating autoantibody profiles in BP show that disease severity often correlates with IgG and/or IgE autoantibody levels (Hashimoto et al., 2017, Iwata et al., 2008). In agreement, BPDAI scores of all study subjects strongly correlated with BP180 IgG levels ($p=0.002$, $r = 0.5850$ for BP CON; $p=0.0212$, $r=0.468$ for ND +BP). In in subjects without neurologic disease, BPDAI scores also correlated moderately with BP180 IgE ($p=0.0173$, $r = 0.3944$).

Relationships between different the different classes/specificities of antibodies were also evaluated. While several correlations were identified in the BP CON group, none were observed when subjects with neurologic disease were considered as a whole, nor were they consistent when broken down by type of neurologic disease. Briefly, BP180 IgG levels correlated moderately with BP180 IgE ($p=0.0187$, $r=0.3491$) in the BP CON group, but instead correlated strongly ($p=0.0279$, $r=0.7857$) with BP230 IgG in the STR + BP group. In contrast, BP230 IgG correlated ($p=0.292$, $r=0.3183$) only with total IgE in the BP CON group. Finally, BP180 IgE levels were inversely associated with both BP230 IgG ($p = 0.0202$, $r=-0.7333$) and BP230 IgE ($p=0.034$, $r=-0.6848$) only in subjects with PD + BP.

DISCUSSION

Preceding neurologic disease is one of the most common comorbidities of BP (Bastuji-Garin et al., 2011, Chen Y. J. et al., 2011, Ren et al., 2017). However, it has not been established whether the clinical phenotype of BP differs in the presence or absence of neurologic disease. In this report, patient demographics and circulating autoantibody levels were examined in BP patients with PD, DEM or STR and BP patients without neurologic disease. The main findings of this study are that BP patients with preceding neurologic disease have a shorter elapsed time between onset of skin disease and BP diagnosis and that subjects with preceding PD or DEM, but not STR, are significantly older than BP patients without neurologic disease. However, no significant differences in clinical presentation, BP severity scores or autoantibody (IgG and IgE) responses were observed amongst the groups.

It is hypothesized that the association between neurologic disease and subsequent BP results from antibodies initially generated in response to the inflammatory processes associated with neurologic disease (Chen J. et al., 2011, Li et al., 2009, Messingham et al., 2016,

Seppänen, 2013). In this scenario, generation of cutaneous autoantibodies is dependent on transit of neuronal proteins and/or sensitized immune cells through the blood brain barrier. Thus, the progression to BP is likely dictated by the nature and timing of these events. We propose that the progression to BP is influenced by a combination of neurodegeneration and inflammation that is unique to each type of neurologic disease. This idea is consistent with a relatively short gap (5.5 years) between cerebral infarction and development of BP compared to a much longer gap (3-18 years) between the initial diagnosis of PD or DEM and the development of BP (Chen J. et al., 2011, Forsti et al., 2016, Simjee et al., 1985, Taghipour et al., 2010). We were unable to reliably ascertain the onset of neurologic disease in this study; however, based on the established age of onset of PD at 60 years (Pagano et al., 2016) and the onset of BP at mean age of 82.7 ± 5.6 years, a gap of 17-27 years is observed here.

Although serum IgG reactivity to brain and/or skin isoforms of BP180 and BP230 has been reported in patients with neurologic disease, it is not known if or how the specificity of these antibodies changes over time or what changes are associated with the development of BP (Chen J. et al., 2011, Foureur et al., 2006, Kokkonen et al., 2017, Messingham et al., 2016). Further, differences in the immunologic mechanisms leading to BP (with or without neurologic disease) could influence the manifestation of disease, autoantibody profiles, or both.

This study found a significantly shorter duration of skin symptoms prior to BP diagnosis in subjects with preceding neurologic disease. Although this observation may be biologically significant, it must be interpreted with caution. In subjects with neurologic disease, the duration of skin symptoms, such as itch, erosions or eczema, could be easily underestimated or go unnoticed by their representatives or caretakers. Indeed, the fact preceding neurologic disease was not associated with any differences in clinical presentation or severity of BP suggests that this may be the case.

In this report, preceding neurologic disease was not associated with any significant differences in the incidence or specificity of the IgG or IgE antibody response, which is in agreement with a previous study that examined only IgG (Gornowicz-Porowska et al., 2017). Additionally, BP180 IgG levels correlated with both the age of BP onset and disease severity regardless of neurologic disease. Thus, although the events leading to the development of cutaneous antibodies might differ, preceding neurologic disease may not alter the pathogenic mechanisms driving BP. In regard to the IgE autoantibody profiles, a larger number of patients are needed to tease out some potential differences associated with type of neurologic disease. Going forward, it would also be interesting to compare serum IgE reactivity to brain isoforms of BP180 and BP230 based the relative abundance of BP230 in the CNS (Brown et al., 1995) and the robust BP230-IgE response found here.

The possibility remains that preceding neurologic disease results in differences in autoantibody specificity that are not evident when the commercially available ELISAs are used. These kits only detect antibodies targeting a relatively small domain of the protein, known as NC16A, since their pathogenicity in BP is well established (Giudice et al., 1993, Zillikens et al., 1997). However, it is widely accepted that BP patients often have serum

reactivity to regions of BP180 that are outside of NC16A (Fairley et al., 2013). Further, the epitope specificity may depend on the protein isoform driving the antibody response. In agreement, differences in serum reactivity to brain- or skin-derived proteins suggest that subjects with neurologic disease (and not BP) recognize different auto-epitopes than BP patients (Foureur et al., 2006, Kokkonen et al., 2017, Messingham et al., 2016). Indeed, a recent study (Tuusa et al., 2018) demonstrated, via epitope mapping of recombinant proteins, that sera from subjects with MS or Alzheimer's disease recognize different regions of the BP180 protein than sera from BP patients. These findings explain why skin symptoms are not observed when BP180 antibodies are observed in patients with ND but not BP. To determine if BP180 and BP230-reactive antibodies play a role in the progression to BP, and if epitope spreading is required for the development of BP, longitudinal studies utilizing detailed epitope mapping of reactive sera from patients with well-characterized neurologic disease are needed.

Since only a fraction of individuals with neurologic disease go on to develop BP, the goal of this study to determine if any specific characteristics of these patients could be discerned. However, other than the timing of disease, we did not see any clinical or serologic phenotype that differentiates patients with neurologic disease compared to those who do not. Further, the medications for neurologic disease are commonly used and have not themselves been associated with BP at this point. Thus, additional studies are needed to further characterize these patients, and as personalized medicine advances, we may be able to identify predictive factors for the development of BP in the context of neurologic disease.

MATERIALS & METHODS

Study subjects

Patients with clinical and histologic characteristics of BP were recruited from the University of Iowa Hospitals and Clinics and written informed consent was obtained in compliance with the guidelines of the Institutional Review Board (IRB #201106752) and the Declaration of Helsinki Accords. A BP diagnosis was confirmed by detection of cutaneous autoantibodies via direct immunofluorescence, BP180/BP230 ELISA or immunoblot against the recombinant extracellular domain of BP180 (Fairley et al., 2013).

A self-reported history and medical records were used to identify preceding neurologic disease. Of the112 BP patients initially identified, two patients diagnosed with an unspecified autoimmune central nervous system disease were excluded. The remaining 110 BP patients were included: 77 BP CON, 11 PD + BP, 11 DEM + BP, and 11STR + BP. The type of DEM, and also the location, number of strokes and elapsed time between the stroke and the onset of BP, was heterogeneous. None of the patients in our database had MS.

Disease severity

Disease severity was scored using the bullous pemphigoid disease area index (BPDAI) (Murrell et al., 2012). Because some patients were enrolled prior to validation of the BPDAI, scores were available only on a subset of patients; 37 BP CON, 11 PD + BP, 9 DEM + BP, and 7 STR + BP.

Serum antibody detection

Serum antibodies were measured only subjects who had not received any prior corticosteroids or immunomodulatory treatment, resulting in the following N's: 47 BP CON, 10 PD + BP, 11 DEM + BP and 8 STR + BP. IgG antibodies specific for BP180 and BP230 were evaluated using commercial ELISAs (MBL International, Woburn, MA). Of note, this study included 9 subjects (7 BP CON, 2 DEM+ BP) who were negative using the BP180 ELISA that targets the immunodominant NC16A region of BP180. BP180 ELISA-negative patients were included in the study if serum IgG reactivity to recombinant full length BP180 was verified with immunoblot (Fairley et al., 2013). Additionally, IgE autoantibodies specific for BP180 and/or BP230 were typically observed in these patients.

Total serum IgE levels were quantified using electrochemiluminescence performed by the institutional pathology laboratory. BP180 (NC16A)-specific IgE was evaluated by ELISA as described (Messingham et al., 2009). BP230-specific IgE was evaluated using the IgG kit with the substitution of an anti-IgE detection antibody that was previously verified as IgE-specific via immunoblot and ELISA.

Statistical Analysis

Statistical analysis was performed with assistance from Dr. Patrick Ten Eyck at the Institute for Clinical and Translational Science Biostatistics Core at the University of Iowa. A chi-square test was used to assess differences in sex ratios. Generalized linear models (GLMs) were used to compare the values of several outcome measures between different groups. Since all outcomes followed a right-skewed distribution, a gamma distribution and log link was specified to provide pairwise group estimates for the ratio of group means along with p-values. SAS 9.4 was used for all GLM analyses. We decided on a type I error rate, α, of 0.05 which necessitates a p-value ≤ 0.0071 for significance, based on the Bonferroni correction for 7 separate comparisons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used:

BP	bullous pemphigoid
neurologic disease	neurologic disease
DEM	dementia
STR	stroke
PD	Parkinson's disease

MS	multiple sclerosis
CON	control
BPDAI	bullous disease area index

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CREDIT STATEMENT

Kelly Messingham played a role in Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Project Administration, Supervision, Visualization, Writing-Original Draft and Writing-Review and Editing.

Adam Miller played a role in Investigation and Writing-Original Draft, Writing-Review and Editing.

Nandekumar Naranyan played a role in Conceptualization, Funding Acquisition, Investigation, Resources, Writing-Review and Editing.

Samuel Connell played a role in Investigation and Validation of data.

Janet Fairley played a role in Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing-Original Draft, Writing-Review and Editing.

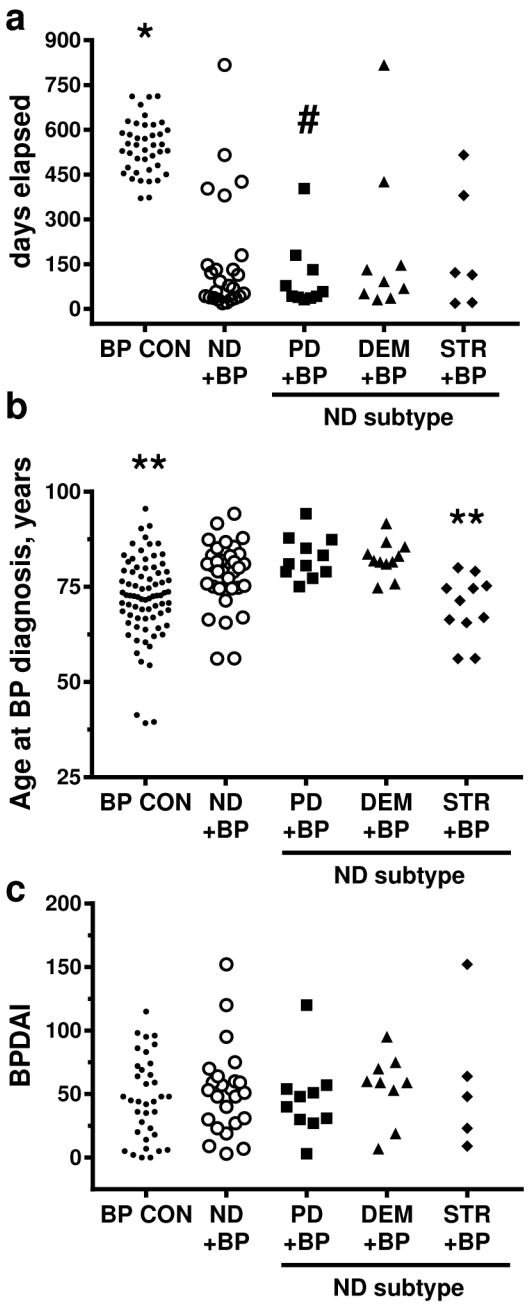

Figure 1. Initial presentation of BP with or without preceding neurologic disease.

Subjects were BP controls (BP CON), and BP patients with preceding neurologic disease (ND); Parkinson's disease (PD+BP), dementia (DEM+BP), stroke (STR+BP). A) Days elapsed was calculated based on the time between the onset of skin symptoms and BP diagnosis; B) Age at BP onset, years; C) Disease severity calculated using the Bullous Disease Area Index (BPDAI). Each point represents an individual patient. Using generalized linear models with a Bonferroni correction a $p \leq 0.0071$ was required for significance; * = vs. all other groups, # = vs. DEM or STR, ** = vs. PD or DEM.

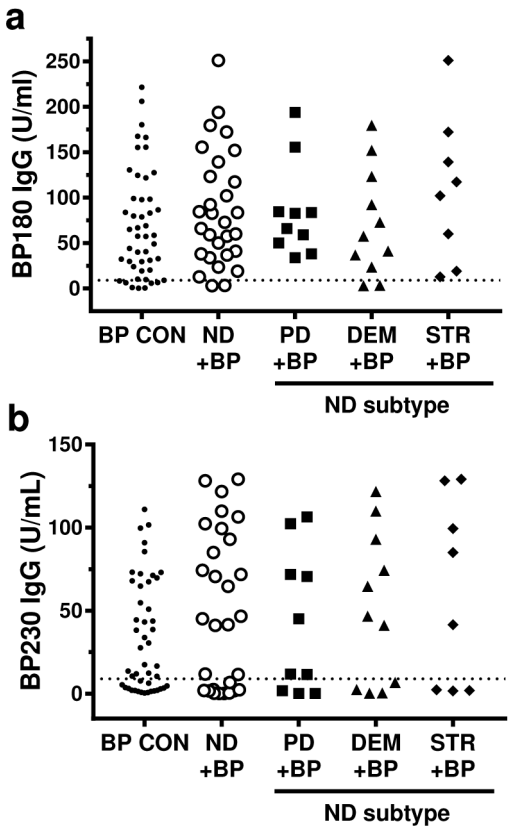

Figure 2. Serum IgG autoantibody levels in BP patients with and without neurologic disease.
Subjects were BP controls (BP CON), and BP patients with preceding neurologic disease (ND); Parkinson's disease (PD+BP), dementia (DEM+BP), stroke (STR+BP). A) BP180- and B) BP230-specific IgG were measured by ELISA. The dashed line indicates the minimum value for a positive test, ≥ 9 Units/ml. Each point represents an individual patient. No statistically significant differences were observed.

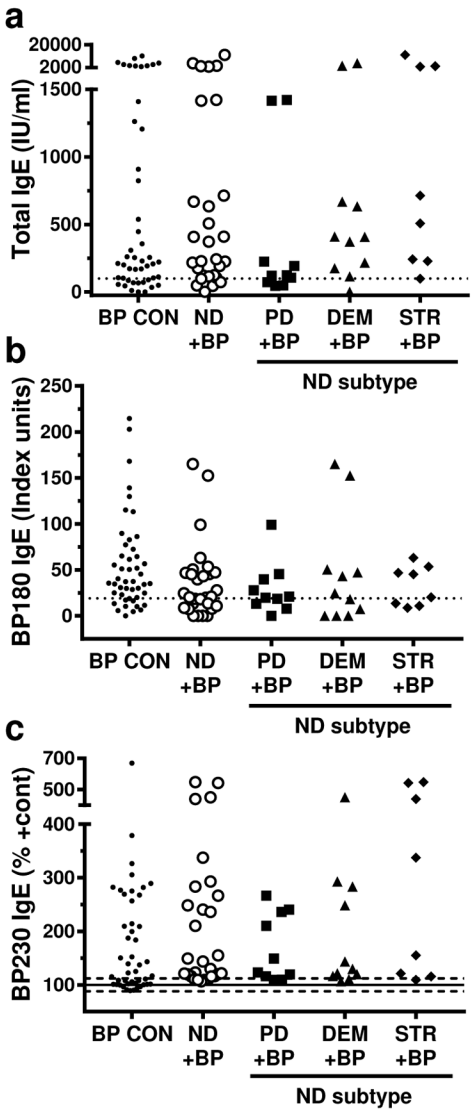

Figure 3. Serum IgE antibody levels in BP patients with and without neurologic disease.

Subjects were BP controls (BP CON), and BP patients with preceding neurologic disease (ND); Parkinson's disease (PD+BP), dementia (DEM+BP), stroke (STR+BP). A) Circulating total IgE was measured with electrochemiluminescence; normal level ≤100 U/ml (dashed line); B) BP180-specific IgE was measured by ELISA, positive test ≥ 19 units/ml; C) BP230-specific IgE was measured by ELISA; mean ± SD is indicated for N = 23 healthy controls is indicated. Each point represents an individual patient. No statistically significant differences were observed.

Table 1:

Analysis of days elapsed, age at diagnosis and BPDAI scores in study subjects.

	Days elapsed [2]		Age at diagnosis, years [3]		BPDAI [3,4]	
Comparison [1]	Mean Ratio [5] *95% CI*	p-value	Mean Ratio 95% CI	p-value	Mean Ratio 95% CI	p-value
ND+BP vs. BP CON	0.515 *0.496-0.534*	**<.0001**	1.085 *1.021-1.124*	0.0085	1.059 *0.707-1.587*	0.7762
PD+BP vs. BP CON	0.333 *0.312-0.355*	**<.0001**	1.146 *1.048-1.252*	**0.0030**	0.935 *0.543-1.610*	0.8042
DEM+BP vs. BP CON	0.661 *0.627-0.696*	**<.0001**	1.143 *1.046-1.249*	**0.0036**	1.120 *0.635-1.974*	0.6911
STR+ BP vs. BP CON	0.624 *0.587-0.663*	**<.0001**	0.965 *0.883-1.055*	0.4297	1.200 *0.582-2.476*	0.6154
PD+BP vs. STR+BP	0.534 *0.491-0.581*	**<.0001**	1.187 *1.056-1.335*	**0.0046**	0.779 *0.340-1.783*	0.5474
DEM+BP vs. STR+BP	1.060 *0.982-1.144*	0.1337	1.184 *1.053-1.331*	**0.0052**	0.933 *0.401-2.168*	0.8693
PD+BP vs. DEM+BP	0.504 *0.466-0.545*	**<.0001**	1.003 *0.892-1.128*	0.9643	0.835 *0.417-1.672*	0.6045

[1] Subjects included BP controls (BP CON), and BP patients with preceding neurologic disease (ND); Parkinson's disease (PD+BP), dementia (DEM+BP), stroke (STR+BP)

[2] calculated based on the interval between the onset of skin symptoms and BP diagnosis. N's = 41 BP CON, 10 PD + BP, 8 DEM + BP, 6 STR + BP.

[3] N's = 77 BP CON, 11 PD + BP, 11 DEM + BP, 11 STR + BP.

[4] Bullous Disease Area Index.

[5] Mean ratio, 95% confidence interval (CI), and p-value are indicated for each comparison. A p-value <0.0071 was considered significant (bold font).

Table 2:

Analysis of serum IgG autoantibodies.

	BP180 IgG [1]		BP230 IgG [1]	
Comparison[2]	**Mean Ratio**[3] ***95% CI***	**p-value**	**Mean Ratio** ***95% CI***	**p-value**
ND+BP vs. BP CON	1.234 *0.788-1.933*	0.3536	1.493 *0.823-2.708*	0.1840
PD+BP vs. BP CON	1.029 *0.626-2.337*	0.5675	1.241 *0.516-2.981*	0.6257
DEM+BP vs. BP CON	1.020 *0.541-1.922*	0.9510	1.500 *0.646-3.487*	0.3408
STR+ BP vs. BP CON	1.560 *0.756-3.217*	0.2249	1.798 *0.687-4.711*	0.2284
PD+BP vs. STR+BP	0.775 *0.316-1.092*	0.5735	0.690 *0.209-2.277*	0.5373
DEM+BP vs. STR+BP	0.654 *0.271-1.575*	0.3387	0.834 *0.259-2.688*	0.7585
PD+BP vs. DEM+BP	1.186 *0.519-2.711*	0.6827	0.827 *0.275-2.484*	0.7314

[1] IgG antibodies specific for BP180 and BP230 were measured by ELISA.

[2] Subjects included BP controls (BP CON), and BP patients with preceding neurologic disease (ND); Parkinson's disease (PD+BP), dementia (DEM+BP), stroke (STR+BP)

[3] Mean ratio, 95% confidence interval (CI), and p-value are indicated for each comparison. A p-value <0.0071 was considered significant.

Table 3:

Analysis of serum IgE antibodies.

	BP180 IgE[2]		BP230 IgE[2]		Total IgE[3]	
Comparison[1]	**Mean Ratio[d] *95% CI***	**p-value**	**Mean Ratio 95% CI**	**p-value**	**Mean Ratio 95% CI**	**p-value**
ND+BP vs. BP CON	0.760 *0.504-1.139*	0.1801	1.195 *0.934-1.530*	0.1540	0.889 *0.443-1.787*	0.7383
PD+BP vs. BP CON	0.581 *0.325-1.038*	0.0661	0.944 *0.665-1.340*	0.7429	0.290 *0.107-0.787*	0.0159
DEM+BP vs. BP CON	1.135 *0.617-2.089*	0.6789	1.084 *0.774-1.519*	0.6331	0.778 *0.297-2.035*	0.6040
STR+ BP vs. BP CON	0.586 *0.318-1.077*	0.0804	1.663 *1.132-2.443*	0.0100	1.792 *0.598-5.372*	0.2933
PD+BP vs. STR+BP	0.992 *0.458-2.150*	0.9844	0.568 *0.353-0.914*	0.0205	0.162 *0.041-0.631*	0.0094
DEM+BP vs. STR+BP	1.939 *0.875-4.296*	0.1013	0.652 *0.409-1.040*	0.0720	0.434 *0.114-1.648*	0.2164
PD+BP vs. DEM+BP	0.512 *0.236-1.109*	0.0884	0.870 *0.561-1.350*	0.5299	0.372 *0.106-1.306*	0.1209

[1]Subjects included BP controls (BP CON), and BP patients with preceding neurologic disease (ND); Parkinson's disease (PD+BP), dementia (DEM+BP), stroke (STR+BP)

[2]IgE autoantibodies specific for BP180 and BP230 were measured by ELISA.

[3]Total IgE was measured electrochemiluminescence.

[4]Mean ratio, 95% confidence interval (CI), and p-value are indicated for each comparison. A p-value <0.0071 was considered significant.