The Association of Bullous Pemphigoid With Cerebrovascular Disease and Dementia

A Case-Control Study

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Objective: To investigate the relationship between bullous pemphigoid (BP) and neurologic disease.

Design: Case-control study.


Participants: Ninety consecutive patients with BP and 141 controls.

Main Outcome Measures: Age-adjusted prevalence of neurologic disease in patients and controls. Time interval between the diagnosis of neurologic disease and BP and type of associated neurologic disease.

Results: At least 1 neurologic diagnosis was present in 42 patients (46%) compared with 16 controls (11%). Patients had significantly increased odds for neurologic diseases regardless of age and sex (crude odds ratio [OR], 6.8; 95% confidence interval [CI], 3.5-13.3; adjusted OR, 6.2; 95% CI, 3.1-12.4). Four major neurologic diagnoses were observed (cerebrovascular disease, dementia, Parkinson disease, and epilepsy), with statistical significance for cerebrovascular disease and dementia (crude OR for cerebrovascular disease, 6.3; 95% CI, 2.8-14.2; adjusted OR, 6.0; 95% CI, 2.6-13.6; crude OR for dementia, 10.7; 95% CI, 2.3-49.0; adjusted OR, 7.9; 95% CI, 1.7-37.3). When accurate data on time of onset of neurologic disease were present (36 of 42 patients [85%]), BP followed neurologic disease in most patients (26 of 36 patients [72%]), with a median interval of 5.5 years.

Conclusion: Bullous pemphigoid is significantly associated with cerebrovascular disease and dementia.

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BULLOUS PEMPHIGOID (BP) IS A debilitating autoimmune skin disease that is characterized by large, tense blisters on the skin of the elderly. It is associated with considerable morbidity and mortality and is the most common immunobullous disease in Europe, with an estimated incidence of 43 per million per year in the United Kingdom1 and 7 to 13 per million per year in other parts of Europe.2,3 The 2 major target antigens are BPAG1, a 230-kDa (BP230) cytoplasmic protein from the plakin family, and BPAG2, a 180-kDa transmembrane glycoprotein (BP180, collagen XVII). Both antigens are components of the hemidesmosomes of the basement membrane zone and play a role in cell-matrix adhesion. Tissue-bound and circulating antibodies of the IgG type recognize the autoantigens and deposit in a linear fashion along the basement membrane zone, leading to a characteristic immunofluorescence picture that is diagnostic of BP.

Over the last 2 decades, various neurologic diseases have been described in association with BP, including cerebrovascular disease, dementia, multiple sclerosis, epilepsy, Parkinson disease, Shy-Drager syndrome, and amyotrophic lateral sclerosis.4-10 The pathomechanism of this relationship is not yet understood and cannot be attributed solely to the elderly age of the patients with BP as some patients in previous studies were middle-aged.4,7,8 Bullous pemphigoid antigens or their isoforms have been identified in brain and neuronal tissue,11,12 and cross-reactivity of autoantibodies with brain and skin and exposure of hidden antigens in brain, triggering an immune response, are possible mechanisms. Two recent epidemiological studies suggested a high prevalence of neurologic disease in patients with BP; dementia and stroke in one uncontrolled study13 and Parkinson disease and multiple sclerosis in the other.9 However, robust epidemiological evidence for the association is lacking. Therefore, we conducted a case-control study to better define the relationship between BP and neurologic disease.
Participants

A total of 90 consecutive patients diagnosed as having BP from 2004 to 2008 were recruited from a specialist outpatient center for immunobullous diseases at a teaching hospital in Oxford, England. The diagnosis of BP was based on characteristic clinical findings and positive results of direct and/or indirect immunofluorescence studies.¹⁴ All patients lived in Oxfordshire, England, and all patients were white Northern Europeans, with the exception of 2 who were from the Indian subcontinent. Patients with a mechanobullous phenotype, scarring, and possible overlap with mucous membrane pemphigoid were excluded. All immunofluorescence studies were carried out on both intact and salt-split skin, and all serum samples, except 3, stained the epidermal side of the split skin. The 3 serum samples that labeled the dermal side did not blot to collagen VII when analyzed with Western blotting. The medical histories of all patients were reviewed for the presence of neurologic disease. Neurologic disease was defined as a confirmed neurologic diagnosis by a hospital physician, neurologist, or psychiatrist; positive imaging findings (computed tomography or magnetic resonance imaging of the brain) when appropriate; or considerable functional disability owing to mental impairment, requiring nursing home care (Karnovsky score ≤50%).¹⁵ A total 141 selected controls without BP or other inflammatory skin disease and with similar age (±5 years) and sex were recruited from a skin tumor clinic in 2007 and 2008. The controls were considered suitable for this study because they were seen in the same outpatient setting and were similar to the case patients in ethnicity (predominantly white Northern Europeans), reflecting the Oxford population. Ethical approval was obtained from the Oxfordshire Clinical Research Ethics Committee (C02.177).

Statistical analysis

Univariate logistic regression was used to calculate the crude odds ratios (ORs) and 95% confidence intervals (CIs) for neurologic disease in relation to BP. Multivariate logistic regression with adjustment for age and sex was used to calculate the adjusted ORs and 95% CIs. The characteristics of the patients with BP and the controls were compared with the Pearson χ² test. The 4 different groups of neurologic diagnoses observed in the series were analyzed separately in the same manner. A 95% CI not containing 1 was statistically significant at P=.05. The Statistical Package for Social Sciences for Windows 16 (SPSS

Table 1. Demographic Characteristics of Patients With Bullous Pemphigoid (BP) and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With BP</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (42)</td>
<td>71 (50)</td>
<td>.28</td>
</tr>
<tr>
<td>Female</td>
<td>52 (57)</td>
<td>70 (49)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>9 (10)</td>
<td>21 (15)</td>
<td>.09</td>
</tr>
<tr>
<td>71-80</td>
<td>26 (29)</td>
<td>56 (40)</td>
<td></td>
</tr>
<tr>
<td>81-90</td>
<td>38 (42)</td>
<td>51 (36)</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>15 (17)</td>
<td>10 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Method

The demographic details of the patients and the controls are presented in Table 1. Forty-two of 90 consecutive patients with BP (46%) had at least 1 neurologic disorder (34 confirmed by a physician or a neurologist and/or imaging findings where appropriate, 4 by a psychiatrist, and 4 with a Karnovsky score <50%) compared with 16 of 141 controls (11%, all confirmed by a physician or a neurologist). The patients with BP had significantly increased odds for neurologic disease compared with the controls (crude OR, 6.8; 95% CI, 3.5-13.3; adjusted OR, 6.2; 95% CI, 3.1-12.4).

Four major neurologic diagnoses were observed (Table 2), and the most common were cerebrovascular disease (30%) and dementia (13%). Parkinson disease and epilepsy were less common in both groups, and the prevalences were not different between cases and controls. The patients with BP had significantly increased odds for cerebrovascular disease and dementia compared with controls (crude OR for cerebrovascular disease, 6.3; 95% CI, 2.8-14.2; adjusted OR, 6.0; 95% CI, 2.6-13.6; crude OR for dementia, 10.7; 95% CI, 2.3-49.0; adjusted OR, 7.9; 95% CI, 1.7-37.3).

The date of onset of neurologic disease could be accurately identified in 36 of 42 patients with BP and neurologic disease (85%), and in most of these patients (26 of 36 [72%]), BP followed the neurologic disease. In 5 patients, the neurologic diagnosis was confirmed after the onset of BP, and 5 other patients received both diagnoses in the same year. The median duration of neurologic disease before the diagnosis of BP was 3.5 years (range, 1-37 years).

Table 2. Prevalences and Spectrum of Neurologic Diagnoses in Patients With Bullous Pemphigoid (BP) and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With BP</th>
<th>Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=90)</td>
<td>(n=141)</td>
<td>Crude</td>
</tr>
<tr>
<td>Any neurologic disease</td>
<td>42 (46)</td>
<td>16 (11)</td>
<td>6.8 (3.5-13.3)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>27 (30)</td>
<td>9 (6)</td>
<td>6.3 (2.8-14.2)</td>
</tr>
<tr>
<td>Dementia</td>
<td>12 (13)</td>
<td>2 (1)</td>
<td>10.7 (2.3-49.0)</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>4 (4)</td>
<td>3 (2)</td>
<td>2.7 (0.6-11.6)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4 (4)</td>
<td>2 (1)</td>
<td>6.5 (0.7-59.2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
<td>2 (1)</td>
<td>2.4 (0.4-14.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

*a Six patients with BP had more than 1 neurologic disease.

*b Adjusted for age and sex.

*c Cerebrovascular disease included stroke, transient ischemic attack, and small-vessel disease.

*d Other neurologic diseases in patients with BP included peripheral neuropathy (n=1), sensorineural deafness (n=1), and motor neuron disease (n=1); and in controls, myasthenia gravis (n=1) and demyelinating disease (n=1).

Inc, Chicago, Illinois) and GraphPad Prism 5 (GraphPad Software Inc, La Jolla, California) were used for data analysis and graphs.
Six patients had more than 1 neurologic diagnosis, and in these 6 patients, the duration of disease was calculated from the first diagnosis. The Figure illustrates the interval between the diagnosis of cerebrovascular disease and dementia and the onset of BP.

The control patients with neurologic disease were older than the patients without neurologic disease, whereas there was no age difference between the patients with BP with and without neurologic disease. The median age of the patients with BP and neurologic disease was 83.5 years (age range, 69-99 years) vs 80 years (age range, 46-98 years) for the patients with BP without neurologic disease (P = .05, Mann-Whitney test) and 84.5 years (age range, 72-98 years) for the controls with neurologic disease vs 78 years (age range, 48-98 years) for the controls without neurologic disease (P = .02, Mann-Whitney test). The male to female ratio in the BP group was 1:1.4; however, the coexistence of neurologic disease was not associated with sex.

To our knowledge, this is the first case-control study to investigate the association of BP and neurologic disease. Our results demonstrate (1) that there is a significantly higher prevalence of neurologic disorders in patients with BP compared with a control group of similar age and (2) that cerebrovascular disease and dementia account for this association. We have found that neurologic disease precedes BP in most cases, as also described in previous reports.4-7,16 Neurologic symptoms may often be subtle, and the onset of disease may be insidious, leading to diagnostic delay. It is therefore likely that the interval between neurologic disease and BP is longer than estimated, and it is tempting to speculate that certain neurologic conditions can predispose to BP.

The incidence and prevalence of neurologic disorders in England have been ascertained in the general population by MacDonald et al.17 The authors showed that 6% of the population had a neurologic disorder at some point in life. Moreover, Prettyman18 reported a prevalence of neurologic disorders in a nondemented cohort of persons older than 65 years, an age range similar to that of patients with BP: the prevalence was 5% for stroke, 3% for epilepsy, and 1% for Parkinson disease. These data accord well with the type and frequency of neurologic disorders observed in our control group and further support the validity of our findings.

In a multicenter epidemiological study in France, Cordel et al13 demonstrated that 36% of consecutive patients with BP had at least 1 neurologic diagnosis. In their case series, the most frequent diagnosis noted was dementia, followed by stroke and Parkinson disease, and there was considerable functional impairment in their patients. In 2005, Stinco et al19 reported a higher prevalence of BP in hospitalized patients with Parkinson disease and multiple sclerosis, but not with stroke or dementia, based on recorded discharge diagnoses compared with an age-matched group treated for trauma. We did not find an association with BP and Parkinson disease, and multiple sclerosis was not observed in our consecutive patients with BP or in our controls.

The limitations of this study include the hospital-based setting involving a tertiary immunobullous disease referral center and therefore a potential referral bias. However, all BP cases included in this study were from Oxfordshire County, and the hospital is the sole provider of dermatology services in the region; therefore, the recruited patients with BP are representative of the local population. All controls were referred to the skin cancer clinic by local general practitioners. Consequently, there is a chance that patients with severe and debilitating neurologic disease were less likely to be referred for skin lesions, in contrast to patients with BP who require specialist dermatology input. However, in the United Kingdom, all suspected skin cancers are referred to dermatologists under the “Improving Outcome Guidance for Skin Cancer,” issued by the National Institute of Clinical Excellence; thus, most suspected skin cancers are seen and treated at 1 site. Selecting a control group from hospital outpatients is also more likely to provide accurate dermatologic and neurologic diagnoses, as full medical notes and all investigations were available for review, and patients with incomplete notes or an uncertain diagnosis were excluded. This systematic approach to medical records also helped avoid the potential bias of an unblinded investigator during a review of the notes.

The link between BP and neurologic diseases could potentially be explained by the presence of an immunologic cross-reactivity between the skin and the brain. Neuronal isoforms of both BP180 and BP230 have been demonstrated in the central nervous system of human and mouse, respectively.11,19-22 and are involved in cytoskeletal stability. Neuronal BP230 (dystonin) knockout mice develop a sensory ataxia known as dystonia musculorum.11 The location and function of dystonin have been studied extensively, whereas less is known about the neuronal BP180 in humans. Moreover, a recent small study showed that serum samples from 3 of 9 patients with BP and cerebrovascular disease reacted with a mouse brain protein that was recognized by a polyclonal antibody to BP230.16 It is plausible to postulate that neurologic disorders may expose these antigens to the immune system and trigger a subsequent
immune response. Many neurologic conditions, in particular cerebrovascular diseases, lead to damage in the blood-brain barrier, which may in turn facilitate autoimmunity toward neuronal antigens and cross-reaction with skin.

The relationship between BP and neurologic disease has been the subject of numerous case reports, but epidemiological data are scarce, and this subgroup of patients with BP have not been further characterized. We have demonstrated that there is a significant association between BP and neurologic disorders, in particular cerebrovascular disease and dementia, and that neurologic disease may be a predisposing factor for BP. The mechanism by which neurologic disease may trigger BP remains obscure and requires further investigation.

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Author Contributions: Dr Taghipour had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Taghipour, Chi, Vincent, Groves, Venning, and Wojnarowska. Acquisition of data: Taghipour and Wojnarowska. Analysis and interpretation of data: Taghipour, Chi, and Wojnarowska. Drafting of the manuscript: Taghipour. Critical revision of the manuscript for important intellectual content: Taghipour, Chi, Vincent, Groves, Venning, and Wojnarowska. Statistical analysis: Taghipour and Chi. Obtained funding: Vincent. Administrative, technical, and material support: Wojnarowska. Study supervision: Groves, Venning, and Wojnarowska.

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REFERENCES