The burden of neurological comorbidities in six autoimmune bullous diseases: a population-based study

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Abstract

Background  Apart from bullous pemphigoid (BP), the association of other autoimmune bullous diseases (AIBDs) with neurological conditions is poorly understood.

Objective  To estimate the association between a wide array of AIBDs and neurological conditions.

Methods  A retrospective cross-sectional study recruited patients with BP, mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita (EBA), pemphigoid gestationis (PG), pemphigus vulgaris (PV) and pemphigus foliaceus (PF).

These patients were compared with their age- and sex-matched control subjects with regard to the lifetime prevalence of Parkinson’s disease (PD), Alzheimer’s disease (AD), stroke, epilepsy and multiple sclerosis (MS). Logistic regression was used to calculate OR for specified neurological disorders.

Results  The current study included 1743, 251, 106, 126, 860 and 103 patients diagnosed with BP, MMP, EBA, PG, PV and PF, respectively. These patients were compared with 10 141, 1386, 606, 933, 5142 and 588 matched controls, respectively. Out of the investigated neurological conditions, PD associated with BP (OR, 2.71; 95% CI, 2.19–3.35); AD with BP (OR, 2.11; 95% CI, 1.73–2.57), MMP (OR, 2.37; 95% CI, 1.03–5.47), EBA (OR, 6.00; 95% CI, 1.90–18.97) and PV (OR, 2.24; 95% CI, 1.40–3.60); stroke with BP (OR, 1.84; 95% CI, 1.55–2.19) and EBA (OR, 2.79; 95% CI, 1.11–7.01); and epilepsy with BP (OR, 2.18; 95% CI, 1.72–2.77) and PV (OR, 1.80; 95% CI, 1.19–2.73). MS did not significantly cluster with any of the six AIBDs.

Conclusion  In addition to BP, EBA and PV were found to cluster with neurological comorbidities. Patients with these AIBDs with compatible symptoms may be carefully assessed for comorbid neurological disorders.

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Conflicts of interest

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Introduction

Autoimmune bullous diseases (AIBDs) represent a group of rare, heterogeneous and potentially life-threatening diseases affecting the skin and/or the mucous membranes. Based on the targeted structures, AIBDs can be categorized into the following large categories: (i) pemphigus diseases with autoantibodies targeting desmosomal adhesion molecules; (ii) pemphigoid diseases with autoantibodies targeting structural proteins of the dermal-epidermal junction.1–3 These diseases impose an elevated burden of morbidity and mortality4,5 and are associated with increased healthcare costs.6,7

A robust association was recently established between bullous pemphigoid (BP), the most frequent subtype of pemphigoid diseases, and a wide array of neurological diseases.8–13 One of the main putative explanations underlying this association was the co-expression of epithelial and neuronal isoforms of BP autoantigens, BP180 and BP230, both in the skin and the central nervous system (CNS), respectively.14 The association of

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neurological comorbidities with other pemphigoid diseases, however, remains to be investigated. Since the BP180 is additionally targeted in other pemphigoid diseases, it is of great interest to assess whether such an association exists in these diseases. The relationship of pemphigus with neurological comorbidities has been poorly investigated, and the current literature is still indecisive about it.\textsuperscript{15,16}

The aim of the current study is to estimate the association of six different AIBDs with the following neurological comorbidities: Parkinson’s disease (PD), Alzheimer’s disease (AD), stroke, epilepsy and multiple sclerosis (MS).

**Methods**

**Study design and database**

The current study was designed as a controlled, cross-sectional, large-scale study utilizing the computerized data set of Techniker Krankenkasse (TK). TK is the largest statutory health insurer in Germany, providing health insurance for 10.7 million inhabitants nowadays and 8.3 million inhabitants in 2012.\textsuperscript{17} Based on the German Social Codebook V, all statutory health insurance companies collect basic data on sociodemographic variables and on comorbidity profile of enrollees.\textsuperscript{17} All data were fully anonymized by the insurer before they were accessed by the authors. Thus, no IRB approval had to be obtained from the local ethics committee.

**Study population**

The database of TK was screened for all prevalent cases with AIBDs between the years 2008 and 2011. All 8.3 million health-insured individuals in this 4-year interval were screened for the presence of a diagnostic code compatible with the following entities: BP, mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita (EBA), pemphigoid gestationis (PG), pemphigus vulgaris (PV) and pemphigus foliaceus (PF). The diagnosis of the aforementioned diseases comprised of 10141, 1386, 606, 933, 5142 and 588 individuals, respectively. The basal demographic characteristics of study participants are detailed in Table S2. At least five control individuals, lacking the diagnosis of any AIBD, were randomly selected for each case patient. That is, six control groups were recruited and matched for the six groups of cases with AIBDs. The control groups were randomly selected from the list of TK members and were matched to cases in accordance with sex and age. Age matching was based on the exact year of birth (1-year strata). Controls were ascertained to be alive and to contribute longitudinal data to TK on the date of their recruitment.

Both case and control participants were systematically checked for the presence of a lifetime diagnosis of the following neurological diseases: PD, AD, stroke (cerebral infarction), epilepsy and MS. The diagnosis of the aforementioned neurological entities relied on the ICD-10 coding system as detailed in Table S1.

**Statistical analysis**

The distribution of sociodemographic and clinical factors was compared between cases and control subjects using the chi-square test. Logistic regression was then utilized to calculate the odds ratio (OR) and 95% confidence interval (CI), to compare cases and controls with regard to the presence of neurological comorbidities. Homogeneity of ORs across strata was tested using Breslow–Day and Tarone’s tests. SPSS software, version 25 (SPSS: IBM Corp, Armonk, NY, USA), was utilized to conduct all statistical analyses.

**Results**

The current study included 1743, 251, 106, 126, 860 and 103 patients diagnosed with BP, MMP, EBA, PG, PV and PF, respectively. The corresponding control groups were recruited and matched for the six groups of cases with AIBDs. The control groups were randomly selected from the list of TK members and were matched to cases in accordance with sex and age. Age matching was based on the exact year of birth (1-year strata). Controls were ascertained to be alive and to contribute longitudinal data to TK on the date of their recruitment.

Both case and control participants were systematically checked for the presence of a lifetime diagnosis of the following neurological diseases: PD, AD, stroke (cerebral infarction), epilepsy and MS. The diagnosis of the aforementioned neurological entities relied on the ICD-10 coding system as detailed in Table S1.

**Table 1** The association of Parkinson’s disease and the different autoimmune bullous diseases

| Disease                        | N of events in cases (%) | N of events in controls (%) | OR (95% CI)   | P value |
|-------------------------------|--------------------------|----------------------------|---------------|---------|
| **Pemphigoid diseases**       |                          |                            |               |         |
| Bullous pemphigoid            | 129/1743 (7.4%)          | 292/10 141 (2.9%)          | 2.71 (2.19-3.35) | <0.001  |
| Mucous membrane pemphigoid    | 8/251 (3.2%)            | 20/1386 (1.4%)             | 2.24 (0.97-5.16) | 0.056   |
| Epidermolysis bullosa acquisita | 5/106 (4.7%)        | 46/606 (7.6%)              | 0.60 (0.23-1.55) | 0.295   |
| Pemphigoid gestationis        | 2/126 (1.6%)            | 14/933 (1.5%)              | 1.06 (0.24-4.71) | 0.940   |
| **Pemphigus diseases**        |                          |                            |               |         |
| Pemphigus vulgaris            | 18/860 (2.1%)           | 81/5142 (1.6%)             | 1.34 (0.80-2.24) | 0.272   |
| Pemphigus foliaceus           | 3/103 (2.9%)            | 6/588 (1.0%)               | 2.91 (0.72-11.83)| 0.135   |

Bold: significant values. CI, confidence interval; N, number; OR, odds ratio.
Table 2 demonstrates the lifetime prevalence of AD among patients with different AIBDs and their controls. AD significantly associated with BP (OR, 2.11; 95% CI, 1.73–2.57; $P < 0.001$), MMP (OR, 2.37; 95% CI, 1.03–5.47; $P = 0.044$), EBA (OR, 6.00; 95% CI, 1.90–18.97; $P = 0.002$) and PV (OR, 2.24; 95% CI, 1.40–3.60; $P < 0.001$). Patients with PF had comparable lifetime prevalence of AD as compared to controls (OR, 1.64; 95% CI, 0.34–8.02; $P = 0.539$), while no cases of AD were registered among patients with PG (Table 2).

When the lifetime prevalence of stroke among case and control groups was examined, the latter was found to cluster with BP (OR, 1.84; 95% CI, 1.55–2.19; $P < 0.001$) and EBA (OR, 2.79; 95% CI, 1.11–7.01; $P = 0.029$; Table 3).

Patients with BP demonstrated more than twofold increased odds of epilepsy (OR, 2.18; 95% CI, 1.72–2.77; $P = 0.005$). Patients with PV (OR, 1.80; 95% CI, 1.19–2.73; $P = 0.005$) displayed a weaker, yet significant, association with epilepsy. MMP, EBA and PF were not significantly associated with epilepsy.

### Table 2 The association of Alzheimer’s disease and the different autoimmune bullous diseases

| Disease                        | N of events in cases (%) | N of events in controls (%) | OR (95% CI) | $P$ value |
|-------------------------------|--------------------------|----------------------------|-------------|-----------|
| **Pemphigoid diseases**       |                          |                            |             |           |
| Bullous pemphigoid            | 142/1743 (8.1%)          | 409/10 141 (4.0%)          | 2.11 (1.73–2.57) | $< 0.001$ |
| Mucous membrane pemphigoid    | 8/251 (3.2%)             | 19/1386 (1.4%)             | 2.37 (1.03–5.47) | 0.044     |
| Epidermolysis bullosa acquisita | 6/106 (5.7%)           | 6/606 (1.0%)               | 6.00 (1.90–18.97) | 0.002     |
| Pemphigoid gestationis        | 0/126 (0.0%)             | 0/933 (0.0%)               | NA          | NA        |
| **Pemphigus diseases**        |                          |                            |             |           |
| Pemphigus vulgaris            | 24/860 (2.8%)            | 65/5142 (1.3%)             | 2.24 (1.40–3.60) | $< 0.001$ |
| Pemphigus foliaceus           | 1/103 (1.0%)             | 5/588 (0.9%)               | 1.14 (0.13–9.89) | 0.903     |

Bold: significant values. CI, confidence interval; N, number; OR, odds ratio.

### Table 3 The association of stroke and the different autoimmune bullous diseases

| Disease                        | N of events in cases (%) | N of events in controls (%) | OR (95% CI) | $P$ value |
|-------------------------------|--------------------------|----------------------------|-------------|-----------|
| **Pemphigoid diseases**       |                          |                            |             |           |
| Bullous pemphigoid            | 190/1743 (10.9%)         | 639/10 141 (6.3%)          | 1.84 (1.55–2.19) | $< 0.001$ |
| Mucous membrane pemphigoid    | 10/251 (4.0%)            | 60/1386 (4.3%)             | 0.92 (0.46–1.82) | 0.803     |
| Epidermolysis bullosa acquisita | 7/106 (6.6%)           | 15/606 (2.5%)              | 2.79 (1.11–7.01) | 0.029     |
| Pemphigoid gestationis        | 1/126 (0.8%)             | 10/933 (1.1%)              | 0.74 (0.09–5.82) | 0.773     |
| **Pemphigus diseases**        |                          |                            |             |           |
| Pemphigus vulgaris            | 42/860 (4.9%)            | 194/5142 (3.8%)            | 1.31 (0.93–1.84) | 0.122     |
| Pemphigus foliaceus           | 1/103 (1.0%)             | 24/588 (4.1%)              | 0.23 (0.03–1.72) | 0.153     |

Bold: significant values. CI, confidence interval; N, number; OR, odds ratio.

### Table 4 The association of epilepsy and the different autoimmune bullous diseases

| Disease                        | N of events in cases (%) | N of events in controls (%) | OR (95% CI) | $P$ value |
|-------------------------------|--------------------------|----------------------------|-------------|-----------|
| **Pemphigoid diseases**       |                          |                            |             |           |
| Bullous pemphigoid            | 96/1743 (5.5%)           | 264/10 141 (2.6%)          | 2.18 (1.72–2.77) | $< 0.001$ |
| Mucous membrane pemphigoid    | 8/251 (3.2%)             | 21/1386 (1.5%)             | 2.14 (0.94–4.89) | 0.071     |
| Epidermolysis bullosa acquisita | 3/106 (2.8%)           | 7/606 (1.2%)               | 2.49 (0.63–9.79) | 0.191     |
| **Pemphigus diseases**        |                          |                            |             |           |
| Pemphigus vulgaris            | 30/860 (3.5%)            | 101/5142 (2.0%)            | 1.80 (1.19–2.73) | 0.005     |
| Pemphigus foliaceus           | 2/103 (1.9%)             | 7/588 (1.2%)               | 1.64 (0.34–8.02) | 0.539     |

CI, confidence interval; N, number; OR, odds ratio. Bold: significant values.
(Table 4). None of the investigated AIBDs was associated with MS (Table S3).

**Discussion**

The current population-based study depicted that PD was over-represented among patients with BP, while AD was associated with BP, MMP, EBA and PV. Stroke was significantly more frequent in BP and EBA, whereas epilepsy was associated with BP and PV. MS was not found to associate with any of the investigated AIBDs.

Several lines of evidence accumulated in the past two decades to shed light on a robust association between BP and neurologic conditions.\(^9\) Even more intriguingly, a significantly higher portion of patients with neurological diseases was tested positive for BP pathogenic autoantibodies,\(^8\) and the levels of these autoantibodies correlated with the severity of dementia.\(^16\) Patients with BP and comorbid neurological conditions were found to experience a more recalcitrant course of BP\(^19\) and to perform an intrathecal synthesis of anti-BP180 and anti-BP230 autoantibodies.\(^20\) In accordance with the current literature, BP demonstrated a significant association with PD, AD, stroke and epilepsy. Although previous studies revealed a well-established association with MS,\(^8\) this comorbidity might not have been detected in our study owing to the rare nature of MS, which necessitate even a larger cohort of BP to be significantly detected.

Since neuronal isoforms of BP180 and BP230, the autoantigens of BP, are expressed in the CNS, it was long assumed that neuroinflammation, accompanying neurological diseases, may expose these antigens to the immune system and result in mounting a cross-reactive immune response against their cutaneous isoforms. Since BP180 is additionally targeted in MMP and PG, it is tempting to assume that these diseases similarly cluster with neurological comorbidities. Our findings indicated that MMP was solely associated with AD, whereas PG, as expected, demonstrated no association with any of the neurological conditions of interest. The lower burden of neurological conditions among patients with MMP and PG despite the immunological similarities with BP may stem from their younger age. Further research is warranted to delineate additional determinants accounting for this difference.

Epidermolysis bullosa acquisita demonstrated a significant association with AD and stroke. While neurological diseases were anecdotally reported to coexist with EBA,\(^21\) no studies were undertaken so far to estimate this comorbidity. The autoantigen of EBA, type VII collagen, was found to be expressed in various normal and pathological cerebral structures, particularly in the cerebellum, pons and medulla.\(^22\)–\(^24\) The hypothesis of a cross-reactive immune response between the neuronal and epithelial isoforms of this autoantigen should be further examined.

Our study revealed that PV clusters with AD and epilepsy. The latter accords with a large-scale population-based Israeli study demonstrating an increased prevalence of dementia, PD and epilepsy among patients with pemphigus, without differentiating between the different subtypes of the disease. In a recent experimental study, Desmoglein (Dsg)-1, the autoantigen of PF and mucocutaneous PV, was found to be expressed in the plasma membrane of oligodendrocytes in the corpus callosum of murine brain.\(^25\) The latter lends weight to an earlier study showing Dsg1-gamma expression on the murine brain.\(^26\) The hypothesis of cross-reactivity between the epithelial and neuronal isoforms of Dsg-1 cannot be thoroughly refuted. Further experimental work is necessary to further comprehend the molecular basis of this epidemiological observation. While patients with PF displayed slightly higher prevalence rates of PD and epilepsy, the latter did not exceed the level of statistical significance due to the relatively small sample size of PF.

The current study enabled to evaluate the epidemiological relationship between six different AIBDs and the main neurological comorbidities. The current findings represent a novel investigation of the comorbidity between neurological diseases and MMP, EBA, PG and the different subtypes of pemphigus. These diseases are typified by a rare nature, which obfuscates the identification of their comorbidities due to the low number of patients enrolled in studies. By utilizing a large data set of 8.3 million enrolles, the current study was statistically powered to detect the coexistence of these rare diseases with uncommon outcomes such as neurological conditions. Although not fully representative of all patients in Germany, results are likely to mirror a realistic image since belonging to a health insurance company is compulsory, and the presence of meaningful selection bias is improbable.

The current study has several limitations to be acknowledged. The diagnosis of AIBDs relied on diagnostic codes rather than on the acceptable immunopathological criteria. However, misclassification of these diseases is unlikely given that performing the necessary immunopathological and immunoserological assays is the common practice across Germany.\(^27\) Owing to the cross-sectional design, the temporal relationship between investigated variables could not be identified, thus interfering with drawing firm conclusions about causality.\(^28\)

In conclusion, the current population-based large-scale study attested that a wide assortment of AIBDs cluster with different neurological conditions. Out of the investigated neurological conditions, PD clustered with BP; AD with BP, MMP, EBA and PV; stroke with BP and EBA; epilepsy with BP and PV. Physicians managing patients with AIBDs should be aware of these associations and refer patients with relevant symptoms for neurological consultations to enable early detection and better management. Experimental research is necessary to better understand the molecular mechanism of this novel observation.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Diagnostic codes of study participants.
Table S2. Basal characteristics of study participants.
Table S3. The association of multiple sclerosis and the different autoimmune bullous diseases.