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Bipolar Disorder Associated with Another Autoimmune Disease—Pemphigus: A Population-based Study

Le trouble bipolaire associé à une autre maladie auto-immune — le pemphigus : une étude dans la population

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Abstract

Objectives: Recent evidence suggests a notable role for inflammation and immune dysregulation in the neuroprogression of bipolar disorders (BD). Several autoimmune comorbidities have been reported in association with BD. However, the epidemiological relationship between pemphigus and BD has not yet been elucidated. We aimed to estimate the association between pemphigus and BD using a large-scale, real-life computerized database.

Methods: Data for this study were retrieved from the database of the Clalit Health Services, the largest, state-mandated, health service organization in Israel. This study was designed as a cross-sectional study. The proportion of patients with BD was compared between patients diagnosed with pemphigus and age-, sex-, and ethnicity-matched control subjects. A logistic regression model was performed to estimate how pemphigus and other covariates contributed as risk factors for BD.

Results: A total of 1,985 pemphigus cases and 9,874 controls were included in the study. The prevalence of BD was greater in cases with pemphigus than in controls (1.0% v. 0.5%, respectively; $P = 0.023$). This coexistence was more prominent among patients of Jewish ethnicity. After controlling for confounders, such as age, sex, ethnicity, socioeconomic status, drug abuse, alcohol abuse, smoking, healthcare utilization, and comorbidities, pemphigus demonstrated a substantial independent association with BD (OR, 1.7; 95% CI, 1.0 to 2.9).

Conclusions: Pemphigus is significantly associated with BD. Patients with pemphigus should be assessed for comorbid BD. Experimental research is needed to better recognize the biological mechanisms underlying this observation.

Abrégé

Objectifs : Des données probantes se sont récemment accumulées qui suggèrent que l'inflammation et la dérégulation immune peuvent jouer un rôle important dans la neuroprogression des troubles bipolaires (TB). Plusieurs comorbidités auto-immunes ont été déclarées en association avec le TB. Toutefois, la relation épidémiologique entre le pemphigus et le TB n'a pas encore été élucidée. Nous cherchions à estimer l'association entre le pemphigus et le TB à l'aide d'une base de données informatisée réelle à grande échelle.

Méthodes : Les données de cette étude ont été extraites des bases de données des Clalit Health Services, la plus grande organisation de services de santé d'État d'Israël. Cette étude a été conçue comme une étude transversale. La proportion de TB a été comparée entre les patients ayant reçu un diagnostic de pemphigus, et des sujets témoins appariés selon l'âge, le sexe,

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et l'origine ethnique. Un modèle de régression logistique a été effectué pour estimer comment le pemphigus et d'autres covariables contribuaient comme facteurs de risque du TB.

Résultats : Un total de 1 985 patients du pemphigus et de 9 874 témoins ont été inclus dans l'étude. La prévalence du TB était plus élevée chez les patients du pemphigus que chez les sujets témoins (1,0 % c. 0,5 %, respectivement; $P = 0{,}023$). Cette coexistence était plus dominante chez les patients d'origine juive. Après contrôle des facteurs de confusion comme l'âge, le sexe, l'origine ethnique, le statut socio-économique, l'abus de drogues, l'abus d'alcool, le tabagisme, l'utilisation des soins de santé, et les comorbidités, le pemphigus démontrait une association indépendante substantielle avec le TB (RC 1,7; IC à 95 % 1,0 à 2,9).

Conclusions : Le pemphigus est significativement associé au TB. Les patients du pemphigus devraient être évalués pour un TB comorbide. Il faut une recherche expérimentale pour mieux reconnaître les mécanismes biologiques sous-jacents de cette observation.

Keywords
Bipolar disorder, pemphigus, autoimmune, inflammation, cytokines

Pemphigus describes a group of organ-specific autoimmune skin diseases characterized by the production of autoantibodies to desmoglein 1 and 3—desmosomal adhesion molecules responsible for maintaining the integrity of the epidermis. The pemphigus group of diseases are mucocutaneous blistering diseases that show a loss of cohesion of epidermal cells (acantholysis), which leads to the formation of clefts in the epidermis and a clinical phenotype of oral ulcerations and superficial vesicles on the skin.[1] Although psychodermatological research on pemphigus is not well established, higher prevalence rates of psychiatric comorbidities have been reported among patients with pemphigus.[2-4] In addition, depression and anxiety have been reported to correlate with disease activity[5] and to persist during periods of remission.[6]

Bipolar disorder (BD) is characterized by alternating periods of mania (or hypomania) and depression, and is now regarded as a multisystem condition, effecting not only mood but also cognitive, endocrine, autonomic, and sleep functions.[7] The prevalence of the disorder is about 4% among the general population, affecting both sexes equally, with an age at onset of $\sim$20 years.[8,9] Patients with BD experience higher rates of cardiovascular, pulmonary, infectious, and metabolic comorbidities, all of which are associated with a decreased life expectancy.[10,11]

Recent evidence suggests that inflammation and immune dysregulation may play a notable role in the neuroprogression of BD.[12] The pathophysiological mechanism accounting for this observation is mediated by chronic inflammation, as increasing neuroinflammation results in neuronal damage.[13] Several autoimmune comorbidities have been reported in association with BD, including Guillain-Barré syndrome,[14] Crohn's disease,[14] autoimmune hepatitis,[14] multiple sclerosis,[15] rheumatoid arthritis,[16,17] autoimmune thyroiditis,[18] and systemic lupus erythematosus.[19] However, the epidemiological relationship between pemphigus and BD has not yet been elucidated.

In a recent work, psychiatric comorbidities were associated with a higher risk of developing bullous pemphigoid (BP), another autoimmune bullous disease.[20] Because BP and pemphigus share a similar pathogenesis involving autoantibody-mediated damage to the epithelial basement membrane zone and epithelial cell-surface antigens, respectively, we sought to investigate whether a similar association exists among patients with pemphigus.

The aim of our study was to investigate the association between pemphigus and BD in a large-scale, cross-sectional study, using one of the largest cohorts of patients with pemphigus in the literature.

Methods

Study Design and Database

The current study was designed as a population-based, cross-sectional study using the database of Clalit Health Services (CHS)—the largest, public health care provider organization in Israel—in the setting of general community clinics, primary care and referral centers, and ambulatory and hospitalized care. The CHS has an inclusive computerized database with continuous real-time input from pharmaceutical, medical, and administrative computerized operating systems that facilitate epidemiological studies. The validity of diagnoses in this registry, which are grounded on reports by hospital and primary care physicians and specialists, was previously identified to be reliable.[21]

Study Population and Covariate Factors

Cases were defined as having pemphigus when there was a documented diagnosis of pemphigus at least twice in the medical records registered by a physician in the community, or when pemphigus was listed in the diagnoses of discharge letters from hospitals. Up to 5 control patients were randomly selected for each case patient. The control group was randomly selected from the list of CHS members matched to cases regarding sex and age, and excluding patients with pemphigus. Age matching was based on the exact year of birth (1-year strata). Controls were ensured to be alive and contributing data to CHS on the date of the diagnosis of the matched case. These diagnoses were extracted from the CHS registry of chronic diseases, which is based on reports from hospital and primary care physicians, and validated by primary physicians. A Charlson comorbidity score was

calculated for each of the study participants. The Charlson index is a weighted index reflecting the degree of comorbidity of a patient by considering the number and seriousness of comorbid disorders. It is a validated method of measuring comorbidity, and a good predictor of outcome.[22] Healthcare utilization was determined by the number of total visits per individual in the year before the diagnosis of pemphigus, and before the enrollment of control subjects.

Statistical Analysis

The distribution of sociodemographic and clinical covariates was compared between patients with and without pemphigus using a Chi-square test for sex and socioeconomic status (SES), and a *t* test for age. The prevalence of psoriasis was investigated within the general study groups, as well as within age, sex, and ethnic subgroups. Crude and Mantel-Haenszel OR, as well as CI are presented. Homogeneity of ORs across strata was tested using Breslow–Day and Tarone's tests. A logistic regression model was used to estimate the association between pemphigus and psoriasis in a multivariate analysis. The vast study sample (which prevented considering it as sparse data) as well as the exact age matching both permitted the use of unconditional logistic regression.[23] The selection of this type of logistic regression was determined to rely on the features of the study regardless of the results. Statistical analysis was performed using SPSS software, version 23 (SPSS, Chicago, IL, USA).

Results

The study included 1,985 patients with pemphigus and 9,874 age-, sex-, and ethnicity-matched control subjects. The mean (SD) age at presentation of pemphigus was 72.1 (18.5) y, which is identical to the age of control subjects at the date of their enrollment. Of the cases, 1,188 (59.8%) were female, with a similar proportion seen in the controls. The ethnic and socioeconomic structure of the 2 groups were similar. Although the prevalence of drug and alcohol abuse was comparable between the 2 groups, there was a higher proportion of smokers among the control subjects. Comorbidity rates, as measured by the Charlson index, were higher in pemphigus cases, with 1,059 (53.4%) having severe comorbidity compared with 4,055 (41.1%) of the controls. Healthcare utilization rates were lower in cases than controls: 65% of cases and 71% of controls had more than 12 consultations in the year before pemphigus diagnosis (Table 1).

The prevalence rate of BD was greater in patients with pemphigus than in control subjects (1.0% v. 0.5%, respectively; OR, 1.8; 95% CI, 1.1 to 3.1; $P = 0.023$). When stratified by age, the association was prominent for patients aged between 40 and 59 y, and older than 80 y. A significant association was also observed among patients of Jewish ancestry (Table 2).

No significant confounding by age, sex, or ethnic background was noted, as the Mantel–Haenszel ORs are within 10% of the crude ORs. No modification-significant effect of the association between pemphigus and BD was noted by any covariate (data not shown).

After controlling for confounders such as age, sex, ethnicity, SES, drug abuse, alcohol abuse, smoking, healthcare utilization, and comorbidities, pemphigus demonstrated a substantial independent association with BD in the multivariable logistic regression analysis (OR, 1.7; 95% CI, 1.0 to 2.9; Table 3). High SES and drug abuse were also found to be associated with BD (Table 3).

Table 1. Descriptive Characteristics of the Study Population.[a]

Characteristic	Patients with pemphigus ($N = 1,985$)	Controls ($N = 9,874$)	*P* value
Age, years			
Mean (SD)	72.1 (18.5)	72.1 (18.5)	NS
Median (range)	77.4 (0-103.0)	77.4 (0-103.1)	
Male sex, N (%)	797 (40.2%)	3,962 (40.1%)	NS
Ethnicity, N (%)			
Jews	1,805 (90.9%)	8,866 (89.8%)	NS
Arabs	180 (9.1%)	1,008 (10.2%)	
Socioeconomic status, N (%)			
Low	634 (31.9%)	3,249 (32.9%)	NS
Intermediate	830 (41.8%)	4,263 (43.2%)	NS
High	423 (21.3%)	2,217 (22.5%)	NS
BMI, kg/m^2, Mean (SD)	27.7 (6.6)	27.9 (6.6)	NS
Smoking, *N* (%)	510 (25.7%)	2,758 (27.9%)	0.045
Drug abuse, *N* (%)	15 (0.8%)	44 (0.4%)	0.073
Alcohol abuse, *N* (%)	23 (1.2%)	84 (0.9%)	NS
Charlson comorbidity score, *n* (%)			
None (0)	344 (17.3%)	2,636 (26.7%)	<0.001
Moderate (1-2)	582 (29.3%)	3,183 (32.2%)	0.011
Severe ($\geq$3)	1,059 (53.4%)	4,055 (41.1%)	<0.001
Healthcare utilization, *n* (%)			
0 visits	286 (14.4%)	770 (7.8%)	<0.001
1-12 visits	411 (20.7%)	2,094 (21.2%)	NS
$\geq$13 visits	1,288 (64.9%)	7,010 (71.0%)	<0.001

[a]SD. Standard deviation; BMI, body mass index.

Discussion

This is the first population-based study aiming to examine the association between pemphigus and BD. Our findings disclose a significant association between pemphigus and BD, with a multivariate OR of 1.7 (95% CI, 1.0 to 2.9). The prevalence rate of BD in patients with pemphigus is notably higher than in age-, sex-, and ethnicity-matched control subjects (1.0% v. 0.5%, respectively; $P = 0.023$).

Psychiatric Comorbidity in Pemphigus

The pemphigus group of diseases inflict significant psychological trauma, and patients with pemphigus experience a significant decrease in their quality of life, among physical, psychological, and social aspects.[5,24-27] However,

Table 2. Stratified Analysis by Age, Sex and Ethnicity Subgroups of the association between Pemphigus and Bipolar Disorder: Univariate Analysis.[a]

Subgroup	Number	Bipolar disorder in patients with pemphigus (*N*=1,985) *N* (%)	Bipolar disorder in controls (*N*=9,874) *N* (%)	OR (95%CI)	*P* value
All	11,859	19 (1.0%)	52 (0.5%)	**1.83 (1.08 to 3.10)**	**0.023**
Age, y					
0-39	872	1 (0.7%)	1 (0.1%)	5.08 (0.32 to 81.75)	NS
40-59	1,768	2 (0.7%)	1 (0.1%)	**10.05 (0.91 to 111.17)**	**0.020**
60-79	4,121	4 (0.6%)	27 (0.8%)	0.74 (0.26 to 2.12)	NS
≥80	5,098	12 (1.4%)	23 (0.5%)	**2.59 (1.29 to 5.24)**	**0.006**
Sex					
Male	4,759	8 (1.0%)	22 (0.6%)	1.82 (0.81 to 4.10)	NS
Female	7,100	11 (0.9%)	30 (0.5%)	1.83 (0.92 to 3.67)	0.08
Ethnicity					
Jews	10,671	18 (1.0%)	51 (0.6%)	**1.74 (1.02 to 2.99)**	**0.041**
Arabs	1,188	1 (0.6%)	1 (0.1%)	5.63 (0.35 to 90.35)	NS

[a]OR, odds ratio; n, Number; CI, confidence interval; NS, non-significant.
Bold: Significant value.

Table 3. Association between Pemphigus and Bipolar Disorder after Controlling for Confounders by Logistic Regression Model.[a]

Variable	OR	95% CI	*P* value
Pemphigus	1.73	**1.01 to 2.94**	**0.045**
Age (per y)	1.01	0.99 to 1.03	0.130
Female sex	1.12	0.68 to 1.85	NS
Jewish ethnicity (v. Arabs)	3.14	0.7 to 12.99	0.114
SES (High v. low)	2.32	**1.10 to 4.92**	**0.028**
SES (High v. intermediate)	1.19	0.70 to 2.05	NS
Drug abuse	5.76	**1.31 to 25.38**	**0.021**
Alcohol abuse	1.04	0.13 to 8.08	NS
Smoking	0.93	0.53 to 1.65	NS
Healthcare utilization	1.00	0.99 to 1.01	NS
Charlson comorbidity score	1.05	0.94 to 1.17	NS

[a]OR, odds ratio; CI, confidence interval; SES, socioeconomic status. NS, non-significant.
Bold: Significant values.

psychiatric comorbidities in pemphigus have not been investigated thoroughly in the past. A recent Israeli study found an increased prevalence of depression among patients with pemphigus relative to matched control subjects.[4] In the study of Kumar et al.,[3] 20 of 50 Indian patients with pemphigus (40%) were screened GHQ-12 positive. Arbabi et al.[2] reported that 157 of 212 Iranian patients with pemphigus scored ≥6 on GHQ-28 bimodal scoring, yielding a 73.7% prevalence of comorbid mental disorder. The association between pemphigus and BD, however, had yet to be explored.

Autoimmune Comorbidities in BD

Inflammatory processes in the periphery and the brain (neuroinflammation) are seemingly incorporated into the pathophysiology of BD.[12] Inflammatory cytokines take part in the multifactorial progressive neuropathological processes in BD and can explain some of the clinical features of BD.[12,28]

Evidence for immunological impairment among patients with BD has been based on studies identifying autoimmune comorbidities with BD. Patients with autoimmune diseases are at a higher risk for BD, and, conversely, patients with BD exhibit a higher incidence of autoimmune comorbidities.[7] In a recent large-scale, Danish population-based, retrospective cohort study, the authors found that patients with a history of Guillain-Barré syndrome, Crohn's disease, or autoimmune hepatitis had a greater risk of developing BD.[14] Women with systemic lupus erythematosus also have a 6-fold increased incidence of BD,[19] and multiple sclerosis patients present up to a 30-fold increase.[15] Moreover, patients with BD have a higher prevalence of autoimmune thyroiditis and anti-thyroid peroxidase antibodies, without a direct relation to lithium exposure.[18]

The Mechanism Underlying the Association between Pemphigus and BD

There is mounting evidence of elevated immune biomarkers, chiefly pro-inflammatory cytokines, in the peripheral and central nervous systems of patients with BD,[7] emphasizing the persistent inflammatory burden among these patients. Chronic inflammation may serve as a possible pathway for BD symptoms among patients with pemphigus. Neuroinflammation is suspected to induce neuronal cellular damage through several mechanisms, including excitotoxicity, oxidative stress, and mitochondrial dysfunction, all of which have been implicated in the development of BD.[12,13]

Brain-reactive autoantibodies are thought to account for the high prevalence of neuropsychiatric symptoms in patients with some form of autoimmune disease.[29-31] This is extremely pertinent in a B-cell–mediated diseases like pemphigus, where autoantibodies are indispensable for the initiation of the disease. Moreover, desmoglein-1, a target autoantigen implicated in the pathogenesis of pemphigus,

was recently found to be expressed in the corpus callosum of mouse models.[32] Because desmoglein-1 is expressed both on the epithelial cell surface and in the central nervous system,[32,33] we cannot rule out a cross-reactivity between its epithelial and neuronal isoforms, and, therefore, the development of brain-reactive autoantibodies.

The Role of Confounding Factors

Significant data demonstrate a high prevalence of drug abuse among patients with BD,[34] and this prevalence is substantially greater than the rates in control subjects or the general population.[35,36] In a recent prospective cohort study, adolescents with BD were significantly more likely to experience higher rates of substance use disorder as compared with control subjects (49% v. 26%, respectively).[37] Our findings, that drug abuse is independently associated with BD with a multivariate OR of 5.8 (95% CI, 1.31 to 25.38), align with these data.

Smoking was highly associated with BD in several studies,[16,38,39] with a prevalence rate of current smoking among individuals with BD ranging from 30% to 70%, approximately 2 to 3 times higher than that in the general population.[39] However, conflicting evidence exists as to whether smoking exerts an adverse effect on the course of BD, and no causal relationship between smoking and BD was established.[16,39] Similarly, in our analysis, smoking was not significantly associated with BD.

Regier et al.[35] have reported that alcohol dependence was twice as likely to co-occur in people with BD than in those with unipolar depression. Helzer and Przybeck[40] found that mania and alcohol abuse are 6.2-fold more likely to occur together than would be expected by chance. In our study, however, we found no independent association between alcohol abuse and BD.

Strengths and Limitations

In addition to our novel findings, the current study used a standardized and large cohort size, providing sufficient power to exclude chance as the basis for the findings and minimize the susceptibility to selection and ascertainment bias, often a central concern in observational studies. The existence of ascertainment bias was further ruled out when our outcome measures were reproduced after adjusting for overutilization of healthcare services.

The cross-sectional design of the study is at the root of its limitation, as we were unable to address the temporal relationship between pemphigus and BD; this therefore interferes with our ability to draw causal links between the 2 entities.[41] As the CHS registry was originally designed for clinical purposes and not for fulfilling formal disease criteria, a validation of the diagnosis of pemphigus or BD is lacking. Nevertheless, specialists are required to affirm diagnoses of pemphigus and BD, which are then added by primary care physicians into the database, and previous studies based on the CHS database have shown a high reliability of the data.[42] Furthermore, the diagnosis of BD is performed by trained psychiatrists, who are the only practitioners legally allowed to treat patients with psychiatric disorders in Israel; therefore, the data registry is likely to be precise and validated. In addition, we did not obtain data concerning the type of BD (bipolar I disorder, bipolar II disorder, cyclothymic disorder, or rapid-cycling), the immunopathologic variant of pemphigus (vulgaris, foliaceus, or paraneoplastic), as well as the clinical characteristics and the severity of the 2 diseases. Thus, there may be some incomplete control over some of the confounding variables. Given that this study deals with prevalence data, it is possible that the observed association also reflects the effect of one variable on the chronicity of the other; patients with pemphigus may have a more chronic BD and vice-versa.

In conclusion, our population-based study reveals a novel association between pemphigus and BD. Patients with pemphigus should be assessed for comorbid psychiatric disorders and be treated appropriately. Further observational studies are warranted to investigate this association in other cohorts, and experimental research is needed to better recognize the biological mechanisms underlying this observation. Further epidemiological studies are warranted to replicate our findings.

Declaration of Conflicting Interests

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