JAMA Dermatology | Original Investigation

Association Between Pemphigus and Neurologic Diseases

Khalaf Kridin, MD; Shira Zelber-Sagi, PhD; Doron Comaneshter, PhD; Arnon D. Cohen, MD, MPh, PhD

Editorial page 264

CME Quiz at jamanetwork.com/learning and CME Questions page 379

IMPORTANCE The association between pemphigus and neurologic diseases was not evaluated systematically in the past. In a recent uncontrolled cross-sectional study, Parkinson disease was found to be significantly associated with pemphigus; in the same study, epilepsy had a nonsignificant association with pemphigus. Several case reports have suggested that pemphigus coexists with multiple sclerosis and dementia.

OBJECTIVE To estimate the association between pemphigus and 4 neurologic conditions (dementia, epilepsy, Parkinson disease, and multiple sclerosis), using one of the largest cohorts of patients with pemphigus.

DESIGN, SETTING, AND PARTICIPANTS A retrospective population-based cross-sectional study was performed between January 1, 2004, and December 31, 2014, using the database of Clalit Health Services, the largest public health care organization in Israel, in the setting of general community clinics, primary care and referral centers, and ambulatory and hospitalized care. A total of 1985 patients with a new diagnosis of pemphigus and 9874 controls were included in the study.

MAIN OUTCOMES AND MEASURES The proportion of dementia, epilepsy, Parkinson disease, and multiple sclerosis was compared between patients diagnosed with pemphigus and age-, sex-, and ethnicity-matched control participants. Logistic regression was used to calculate odds ratios (ORs) for dementia, epilepsy, Parkinson disease, and multiple sclerosis. The association was examined after a sensitivity analysis that included only patients treated with long-term, pemphigus-specific medications (corticosteroids, immunosuppressants, or rituximab) and after adjustment for several confounding factors.

RESULTS When comparing the 1985 cases (1188 women and 797 men; mean [SD] age, 72.1 [18.5] years) with the 9874 controls (5912 women and 3962 men; mean [SD] age, 72.1 [18.5] years), dementia was seen in 622 cases (31.3%) vs 1856 controls (18.8%), with an OR of 1.97 (95% CI, 1.77-2.20). Epilepsy was present in 74 cases (3.7%) vs 210 controls (2.1%), with an OR of 1.78 (95% CI, 1.36-2.33). Parkinson disease was seen in 175 cases (8.8%) vs 437 controls (4.4%), with an OR of 2.09 (95% CI, 1.74-2.51). Multiple sclerosis was present in 2 cases (0.1%) vs 6 controls (0.01%), with an OR of 1.65 (95% CI, 0.34-8.22). Study findings were robust to sensitivity analysis that included patients receiving pemphigus-specific treatments. Estimates were not altered significantly after controlling for comorbidities and overuse of health care.

CONCLUSIONS AND RELEVANCE An association was observed between pemphigus and specific neurologic diseases, including dementia, Parkinson disease, and epilepsy. Physicians treating patients with pemphigus should be aware of this possible association. Patients with pemphigus should be carefully assessed for comorbid neurologic disorders and receive appropriate treatment.

Author Affiliations: Department of Dermatology, Rambam Health Care Campus, Haifa, Israel (Kridin); School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel (Zelber-Sagi); Department of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel (Comaneshter, Cohen); Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheeva, Israel (Cohen).

Corresponding Author: Khalaf Kridin, MD, Department of Dermatology, Rambam Health Care Campus, PO Box 9602, Haifa 31096, Israel (dr_kridin@hotmail.com).

JAMA Dermatol. 2018;154(3):281-285. doi:10.1001/jamadermatol.2017.5799
Published online February 16, 2018.

Pemphigus is a rare intraepithelial autoimmune blistering disease characterized by painful vesiculobullous lesions on the skin and mucous membranes. It is mediated by IgG autoantibodies against both desmoglein (Dsg) 3 (pemphigus vulgaris) and Dsg 1 (pemphigus foliaceus) transmembrane glycoprotein cadherins responsible for intercellular adhesion of epidermal keratinocyte. These antibodies bind to keratinocyte desmosomes, causing loss of cell-to-cell adhesion and blister formation through a process termed *acantholysis*, whether by a direct effect on desmosomal adherens or by triggering a cellular process that results in acantholysis.[1,2]

In a recent large cross-sectional study examining comorbidities among patients with pemphigus, Parkinson disease was significantly associated with pemphigus, with a multivariate odds ratio (OR) of 1.6 (95% CI, 1.2-2.1).[3] In the same study, epilepsy showed a near-significant association with pemphigus (OR, 1.2; 95% CI, 1.0-1.4) and was significantly associated with the disease among children (P = .003). Moreover, there have been several case reports suggesting that pemphigus coexists with multiple sclerosis (MS)[4-6] and dementia.[7]

Evidence has recently accumulated suggesting an association between bullous pemphigoid, another autoimmune blistering disease, and neurologic conditions.[8-12] Since both bullous pemphigoid and pemphigus share similar pathogenesis involving autoantibody-mediated damage to the epithelial basement membrane zone in bullous pemphigoid and to epithelial cell surface antigens in pemphigus, it is of interest to investigate whether a similar association with neurologic diseases exists among patients with pemphigus. The primary end point of the current study is to test the hypothesis that there is an association between pemphigus and neurologic diseases using one of the largest cohorts of patients with pemphigus reported so far.

Key Points

Question Is there an association between pemphigus and neurologic diseases?

Findings This population-based cross-sectional study of 1985 patients with pemphigus revealed a statistically significant comorbidity between pemphigus and epilepsy, dementia, and Parkinson disease. This association retained its statistical significance after multivariable and sensitivity analyses.

Meaning Clinicians should be aware of this association; further research is warranted to elucidate the mechanism of this link.

Methods

Study Design and Database

We performed a retrospective population-based cross-sectional study from January 1, 2004, to December 31, 2014. Data-mining techniques were used to access information from the Clalit Health Services (CHS) database. Clalit Health Services is the largest managed care organization in Israel, serving a population of approximately 4 500 000 enrolleees in 2016. Clalit Health Services has an inclusive computerized database with continuous real-time input from pharmaceutical, medical, and administrative computerized operating systems that facilitates epidemiologic studies, such as the current analysis. The validity of diagnoses in this registry, which are grounded on hospital reports as well as reports from primary care physicians and specialists, has been shown to be reliable.[13] The CHS database undergoes a continuous validation process by logistic checks (such as comparing the diagnoses from various sources) as well as by direct validation of the diagnoses by each patient's treating physician. This study was approved by the institutional ethics boards of Ben-Gurion University and CHS. Informed consent was not warranted since the data are anonymized and because this is a noninterventional observational study that does not require informed consent according to Israeli law.

Study Population and Covariate Factors

Patients were defined as having pemphigus or each of the 4 neurologic conditions being studied when there was a documented diagnosis of these entities at least twice in the medical records registered by a physician in the community or when they were listed in the diagnoses of discharge letters from hospitals. Up to 5 control participants were randomly selected for each case patient. The control group was randomly selected from the list of CHS members matched with cases regarding sex, age, and ethnicity and after 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. An index date was assigned to each control participant, which was the date of diagnosis of the matched case patient. As pemphigus vulgaris is characterized by an evident ethnic predisposition, data regarding the ethnic background of patients were assessed to ascertain that it did not influence the outcome measures. The ethnicity was classified in accordance with the administrative sector to which the patient belongs.

Data available from the CHS database included age, sex, socioeconomic status, and diagnoses of chronic diseases. These diagnoses were extracted from the CHS registry on chronic diseases, which is based on data from hospital and primary care physicians' reports and validated by primary care physicians. A Charlson comorbidity score was calculated for each of the study participants.[14]

Statistical Analysis

The distribution of sociodemographic and clinical factors was compared between patients with and without pemphigus using the χ^2 test for sex and socioeconomic status and the t test for age. Logistic regression was then used to calculate ORs and 95% CIs to compare cases and controls with respect to the specified neurologic diseases. Homogeneity of ORs across strata was tested using Breslow-Day and Tarone tests. The exact age matching permitted the use of unconditional logistic regression.[15]

Outcome measures were adjusted for comorbidities as determined using Charlson comorbidity scores, excluding the neurologic component of this index—specifically dementia,

hemiplegia, and stroke. Outcome measures were also adjusted for overuse of health care services to ensure that observed associations were not merely owing to increased ascertainment. Health care use was determined by the number of total visits per individual in the year before the diagnosis of pemphigus in cases and pseudodiagnosis in controls. Sensitivity analyses were undertaken, repeating analyses including only cases prescribed the following medications specific for pemphigus for more than 6 months: systemic corticosteroids, adjuvant immunosuppressants (azathioprine, mycophenolate mofetil, or cyclophosphamide), or 1 or more cycle of rituximab.

All statistical analysis was performed using SPSS software, version 18 (SPSS Inc). $P < .05$ (2-sided) was considered significant. Assuming Parkinson disease is present in 2% of controls[16] and 3% of cases, this study has 100% power to detect significant associations between pemphigus and Parkinson disease.

Results

Our study consisted of 1985 patients with incident pemphigus and 9874 age-, sex-, and ethnicity-matched control participants (**Table 1**). The mean (SD) age of patients at presentation of pemphigus was 72.1 (18.5) years, which is identical to the age of the control participants at the date of their enrollment. In all, 797 case patients were male (40.2%) and a similar proportion was seen in controls (3962 [40.1%]). The ethnic and the socioeconomic structure of the 2 groups was also similar. Comorbidity rates, measured by the Charlson comorbidity index, were higher in cases, with 1059 patients (53.4%) having severe comorbidity (score, ≥3) compared with 4055 controls (41.1%).

Table 2 demonstrates the proportions of cases and controls with neurologic diseases stratified by sex and age category. Of 1985 cases, neurologic diseases were present as follows: 622 patients (31.3%) had dementia, 74 (3.7%) had epilepsy, 175 (8.8%) had Parkinson disease, and 2 (0.1%) had MS. Among the control cohort, 1856 participants (18.8%) had dementia, 210 (2.1%) had epilepsy, 437 (4.4%) had Parkinson disease, and 6 (0.1%) had MS.

Table 3 presents the results of the univariate and logistic regression models and summarizes ORs for neurologic conditions in patients with pemphigus and controls across the entire study sample. There was a 2-fold increase in the odds of dementia (OR, 1.97; 95% CI, 1.77-2.20), epilepsy (OR, 1.78; 95% CI, 1.36-2.33), and Parkinson disease (OR, 2.09; 95% CI, 1.74-2.51) among patients with pemphigus relative to control participants. No significant association was established between pemphigus and MS (OR, 1.65; 95% CI, 0.34-8.22; $P = .53$).

Adjusting for comorbidity did not remove any of the significant associations (Table 3). Rates of health care use were higher in cases than in controls, with 7010 controls (71.0%) and 1288 cases (64.9%) having more than 12 consultations in the year prior to diagnosis of pemphigus (Table 1). Adjustment for use of health services did not interfere with any of the above-mentioned associations. In a sensitivity analysis including only cases receiving specific therapy for pemphigus, the previous 3 significant associations persisted without remarkable change of their strength (Table 3).

Table 1. Descriptive Characteristics of the Study Population

Characteristic	Patients With Pemphigus (n = 1985)	Controls (n = 9874)	*P* Value
Age, y			
Mean (SD)	72.1 (18.5)	72.1 (18.5)	>.99
Median (range)	77.4 (0-103.0)	77.4 (0-103.1)	
Male sex, No. (%)	797 (40.2)	3962 (40.1)	.93
Ethnicity, No. (%)			
Jews	1805 (90.9)	8866 (89.8)	.14
Arabs	180 (9.1)	1008 (10.2)	
Body mass index, mean (SD)[a]	27.7 (6.6)	27.9 (6.6)	.36
Smoking, No. (%)	510 (25.7)	2758 (27.9)	.045
Charlson comorbidity score, No. (%)			
None (0)	344 (17.3)	2636 (26.7)	<.001
Moderate (1-2)	582 (29.3)	3183 (32.2)	.01
Severe (≥3)	1059 (53.4)	4055 (41.1)	<.001
Health care use, No. (%)			
0 Visits	286 (14.4)	770 (7.8)	<.001
1-12 Visits	411 (20.7)	2094 (21.2)	.25
≥13 Visits	1288 (64.9)	7010 (71.0)	<.001
Socioeconomic status, No. (%)			
Low	634 (31.9)	3249 (32.9)	.39
Intermediate	830 (41.8)	4263 (43.2)	.25
High	423 (21.3)	2217 (22.5)	.24

[a] Calculated as weight in kilograms divided by height in meters squared.

Discussion

To our knowledge, this is the first population-based study aiming to examine the association between pemphigus and neurologic diseases. Our findings revealed a 2-fold higher prevalence rate of dementia, epilepsy, and Parkinson disease among patients with pemphigus compared with age-, sex-, and ethnicity-matched control participants. Multiple sclerosis was not associated with pemphigus in our analysis.

These findings are concordant with the results of a previous cross-sectional retrospective study reviewing 6406 admissions with a diagnosis of pemphigus in the United States across 11 years, which disclosed a significant association between pemphigus and Parkinson disease and a near-significant association between pemphigus and epilepsy.[3] Case reports have shown the coexistence of pemphigus with MS,[4-6] dementia,[7] and epilepsy[17,18] in individual patients. Nevertheless, a recent retrospective cohort study from Singapore found no significant association between pemphigus and neurologic conditions.[19] The external validity of the latter study is hampered by its small sample size (n = 36).

At least 13 different antigens residing in the central or peripheral nervous system but also in the skin or kidneys

Table 2. Demographics of Cases and Controls With Neurologic Diseases

Characteristic	Participants, No. (%)							
	Dementia (n = 2478)		Epilepsy (n = 284)		Parkinson Disease (n = 612)		Multiple Sclerosis (n = 8)	
	Pemphigus (n = 1985)	Control (n = 9874)	Pemphigus (n = 1985)	Control (n = 9874)	Pemphigus (n = 1985)	Control (n = 9874)	Pemphigus (n = 1985)	Control (n = 9874)
All (n = 11 859)	622/1985 (31.3)	1856/9874 (18.8)	74/1985 (3.7)	210/9874 (2.1)	175/1985 (8.8)	437/9874 (4.4)	2/1985 (0.1)	6/9874 (0.1)
Male (n = 4759)	216/797 (27.1)	619/3962 (15.6)	38/797 (4.8)	87/3962 (2.2)	75/797 (9.4)	215/3962 (5.4)	1/797 (0.1)	1/3962
Female (n = 7100)	406/1188 (34.2)	1237/5912 (20.9)	36/1188 (3.0)	123/5912 (2.1)	100/1188 (8.4)	222/5912 (3.8)	1/1188 (0.1)	5/5912 (0.1)
Age category, y								
<40 (n = 872)	1/144 (0.7)	0/728	3/144 (2.1)	12/728 (1.6)	0/144	1/728 (0.1)	0/144	1/728 (0.1)
40-59 (n = 1768)	1/295 (0.3)	6/1473 (0.4)	5/295 (1.7)	20/1473 (1.4)	1/295 (0.3)	11/1473 (0.7)	0/295	2/1473 (0.1)
60-79 (n = 4121)	161/687 (23.4)	390/3434 (11.4)	30/687 (4.4)	75/3434 (2.2)	51/687 (7.4)	116/3434 (3.4)	2/687 (0.3)	2/3434 (0.1)
≥80 (n = 5098)	459/859 (53.4)	1460/4239 (34.4)	36/859 (4.2)	103/4239 (2.4)	123/859 (14.3)	309/4239 (7.3)	0/859	1/4239 (0.02)

Table 3. Association Between Pemphigus and Neurologic Diseases

Disease	Participants, No. (%)		OR (95% CI)	Univariate *P* Value	OR (95% CI)		
	Pemphigus (n = 1985)	Controls (n = 9874)			Sensitivity Analysis	Adjusted[a]	Adjusted[b]
Dementia	622 (31.3)	1856 (18.8)	1.97 (1.77-2.20)	<.001	1.86 (1.65-2.09)	1.87 (1.67-2.08)	2.04 (1.83-2.28)
Epilepsy	74 (3.7)	210 (2.1)	1.78 (1.36-2.33)	<.001	1.83 (1.37-2.45)	1.72 (1.31-2.25)	1.74 (1.33-2.28)
Parkinson disease	175 (8.8)	437 (4.4)	2.09 (1.74-2.51)	<.001	2.11 (1.73-2.58)	1.97 (1.64-2.36)	2.10 (1.75-2.53)
Multiple sclerosis	2 (0.1)	6 (0.06)	1.65 (0.34-8.22)	.53	1.67 (0.36-8.20)	1.78 (0.36-8.89)	1.32 (0.26-6.68)

Abbreviation: OR, odds ratio.

[a] Adjusted for Charlson Comorbidity Index score, not including neurologic diseases.

[b] Adjusted for health care use.

have now been shown to be targeted by IgG4, including the desmogleins targeted by pemphigus autoantibodies.[20] In an experimental study, Dsg1 was found to be expressed in the corpus callosum of the mouse brain and was localized around the plasma membrane regions of oligodendrocytes.[21] The latter lends weight to an earlier study demonstrating that murine Dsg1-γ expression is not restricted to the skin, as it is also expressed in the brain, skeletal muscle, and liver, among other tissues.[22] In bullous pemphigoid, an obvious association with neurologic conditions has been established.[8-12] One of the most accepted explanations for this association is the cross-reactivity between the neuronal and epithelial isoforms of BP230,[23,24] a cytoplasmic component of hemidesmosomes that belongs to the plakin family of cytolinkersone and 1 of the 2 autoantigens involved in the pathogenesis of bullous pemphigoid.[25] Given that Dsg1 is expressed both on the epithelial cell surface and central nervous system,[21,22] the hypothesis of cross-reactivity between its epithelial and neuronal isoforms cannot be thoroughly excluded. Further experimental work is required to understand the molecular basis of this association.

A genetic predisposition might be considered with regard to the association between pemphigus and Parkinson disease, as both diseases are more frequent among the Ashkenazi Jewish population.[26,27] Patients of Jewish ancestry constitute 90.9% of our pemphigus cohort (n = 1805). Although it was not feasible to differentiate between Jewish individuals of Ashkenazi vs Sephardic extractions, we assume that most belong to the former group, as was previously demonstrated by previous Israeli pemphigus cohorts.[27-30]

Strengths and Limitations

Our study is grounded on a representative computerized database of 4.4 million enrollees over 11 years; thus, it is less susceptible to selection and ascertainment bias than studies from tertiary centers. We used one of the largest cohorts of patients with pemphigus reported so far, giving us the power to exclude chance as the basis for the study findings. This ability to exclude chance is of great importance, as data collection in pemphigus is difficult owing to rarity of the disease and the limited number of patients available for study. The lack of large-scale clinical data is an impediment to a better understanding of pemphigus associations and comorbidities.

The study limitations include the lack of data concerning the immunopathologic subtype of pemphigus (vulgaris, foliaceus, or paraneoplastic), clinical characteristics, and severity. Second, the date of diagnosis of the neurologic comorbidities was not available for the current study. Hence, we could not address the temporal associations between pemphigus and comorbidities, and limited conclusions should be drawn regarding a causal association between the entities.[31] Third, the use of routinely collected "real-life"

data means that direct validation of diagnoses and elimination of cases of misclassification was not feasible. However, if misclassification did occur, it would be nondifferential and might lead to a null bias. Pemphigus in Israel is uncommonly encountered in general practice, and the diagnosis is usually carried out in secondary and tertiary care facilities, relying on skin biopsies and direct and indirect immunofluorescence[27]; therefore, it is very likely to be precise and validated. All of the significant associations were reproduced in a sensitivity analysis including case patients receiving pemphigus-specific treatments, which further lends credence to our observations and argues against the existence of bias. The existence of ascertainment bias was ruled out when our outcome measures were reproduced after the adjustment for overuse of the health care system. Although there is a possibility of overdiagnosis of neurologic disease, it is less likely for pemphigus owing to its rarity and specificity of diagnosis in secondary and tertiary care. Fourth, the study was not sufficiently powered to determine an association between pemphigus and MS. Larger longitudinal studies are needed to address this concern.

Conclusions

Our population-based, cross-sectional study found an association between pemphigus and neurologic conditions—specifically, dementia, epilepsy, and Parkinson disease. Physicians who care for patients with pemphigus should be aware of this association. Further observational research is necessary to examine the temporality of this association and explore the existence of causality. Experimental research is necessary to better understand the molecular mechanism of this novel observation.

ARTICLE INFORMATION

Accepted for Publication: October 20, 2017.

Published Online: February 16, 2018. doi:10.1001/jamadermatol.2017.5799

Author Contributions: Drs Kridin and Cohen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kridin, Zelber-Sagi, Cohen.
Acquisition, analysis, or interpretation of data: Kridin, Comaneshter, Cohen.
Drafting of the manuscript: Kridin.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kridin, Comaneshter, Cohen.
Administrative, technical, or material support: Cohen.
Study supervision: Kridin, Zelber-Sagi, Cohen.

Conflict of Interest Disclosures: None reported.

Meeting Presentation: This paper was presented at the Annual Meeting of the American Academy of Dermatology; February 16, 2018; San Diego, California.

REFERENCES

1. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med*. 2006;355(17):1800-1810.

2. Sitaru C, Zillikens D. Mechanisms of blister induction by autoantibodies. *Exp Dermatol*. 2005;14(12):861-875.

3. Hsu DY, Brieva J, Sinha AA, Langan SM, Silverberg JI. Comorbidities and inpatient mortality for pemphigus in the USA. *Br J Dermatol*. 2016;174(6):1290-1298.

4. Friedel J, Jeandel C, Abensour M, Heid E. Multiple sclerosis and autoimmune skin bullae: a case of pemphigus vulgaris. *Dermatologica*. 1987;175(3):159-160.

5. Belniak E, Stelmasiak Z, Papuć E. Multiple sclerosis and other autoimmune diseases [in Polish]. *Neurol Neurochir Pol*. 2007;41(3):259-266.

6. Estruch BC. Comorbilidad en esclerosis múltiple y su abordaje asistencial. *Med Clin (Barc)*. 2014;143(suppl 3):13-18.

7. Siqueira-Neto JI, Sales PMG, Sobreira EST, et al. Vascular cognitive impairment in *Pemphigus vulgaris*. *Dement Neuropsychol*. 2012;6(3):192-195. doi:10.1590/S1980-57642012DN06030014

8. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: a population-based case-control study. *J Invest Dermatol*. 2011;131(3):631-636.

9. Cordel N, Chosidow O, Hellot M-F, et al; French Study Group of Bullous Diseases. Neurological disorders in patients with bullous pemphigoid. *Dermatology*. 2007;215(3):187-191.

10. Nielsen NM, Frisch M, Rostgaard K, et al. Autoimmune diseases in patients with multiple sclerosis and their first-degree relatives. *Mult Scler*. 2008;14(6):823-829.

11. Jedlickova H, Hlubinka M, Pavlik T, Semradova V, Budinska E, Vlasin Z. Bullous pemphigoid and internal diseases—a case-control study. *Eur J Dermatol*. 2010;20(1):96-101.

12. Gambichler T, Segert H, Höxtermann S, Schmitz L, Altmeyer P, Teegen B. Neurological disorders in patients with bullous pemphigoid. *J Eur Acad Dermatol Venereol*. 2015;29(9):1758-1762.

13. Rennert G, Peterburg Y. Prevalence of selected chronic diseases in Israel. *Isr Med Assoc J*. 2001;3(6):404-408.

14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

15. Pearce N. Analysis of matched case-control studies. *BMJ*. 2016;352:i969.

16. Chillag-Talmor O, Giladi N, Linn S, et al. Use of a refined drug tracer algorithm to estimate prevalence and incidence of Parkinson's disease in a large israeli population. *J Parkinsons Dis*. 2011;1(1):35-47.

17. Caproni M, Torchia D, Parigi L, Fabbri P. Brugada syndrome, epilepsy and pemphigus vulgaris. *South Med J*. 2008;101(11):1183.

18. Labidi A, Serghini M, Karoui S, Ben Mustapha N, Boubaker J, Filali A. Epilepsy, pemphigus and celiac disease. *Tunis Med*. 2014;92(8-9):585-586.

19. Phuan ZYC, Yew YW, Tey HL. Pemphigus and nonassociation with antecedent neurological diseases. *Int J Dermatol*. 2017;56(5):e96-e97.

20. Huijbers MG, Querol LA, Niks EH, et al. The expanding field of IgG4-mediated neurological autoimmune disorders. *Eur J Neurol*. 2015;22(8):1151-1161.

21. Miyata S, Yoshikawa K, Taniguchi M, et al. Sgk1 regulates desmoglein 1 expression levels in oligodendrocytes in the mouse corpus callosum after chronic stress exposure. *Biochem Biophys Res Commun*. 2015;464(1):76-82.

22. Kljuic A, Christiano AM. A novel mouse desmosomal cadherin family member, desmoglein 1γ. *Exp Dermatol*. 2003;12(1):20-29.

23. Li L, Chen J, Wang B, Yao Y, Zuo Y. Sera from patients with bullous pemphigoid (BP) associated with neurological diseases recognized BP antigen 1 in the skin and brain. *Br J Dermatol*. 2009;160(6):1343-1345.

24. Brown A, Bernier G, Mathieu M, Rossant J, Kothary R. The mouse dystonia musculorum gene is a neural isoform of bullous pemphigoid antigen 1. *Nat Genet*. 1995;10(3):301-306.

25. Borradori L, Sonnenberg A. Structure and function of hemidesmosomes: more than simple adhesion complexes. *J Invest Dermatol*. 1999;112(4):411-418.

26. Liu X, Cheng R, Verbitsky M, et al. Genome-wide association study identifies candidate genes for Parkinson's disease in an Ashkenazi Jewish population. *BMC Med Genet*. 2011;12(1):104.

27. Kridin K, Zelber-Sagi S, Khamaisi M, Cohen AD, Bergman R. Remarkable differences in the epidemiology of pemphigus among two ethnic populations in the same geographic region. *J Am Acad Dermatol*. 2016;75(5):925-930.

28. Mimouni D, Bar H, Gdalevich M, Katzenelson V, David M. Pemphigus—analysis of epidemiological factors in 155 patients. *J Eur Acad Dermatol Venereol*. 2008;22(10):1232-1235.

29. Pisanti S, Sharav Y, Kaufman E, Posner LN. Pemphigus vulgaris: incidence in Jews of different ethnic groups, according to age, sex, and initial lesion. *Oral Surg Oral Med Oral Pathol*. 1974;38(3):382-387.

30. Baum S, Astman N, Berco E, Solomon M, Trau H, Barzilai A. Epidemiological data of 290 pemphigus vulgaris patients. *Eur J Dermatol*. 2016;26(4):382-387.

31. Höfler M. The Bradford Hill considerations on causality: a counterfactual perspective. *Emerg Themes Epidemiol*. 2005;2:11.