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ORIGINAL ARTICLE

Association between schizophrenia and an autoimmune bullous skin disease-pemphigus: a population-based large-scale study

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Aims. Immunological hypotheses have become increasingly prominent suggesting that autoimmunity may be involved in the pathogenesis of schizophrenia. Schizophrenia was found to be associated with a wide range of autoimmune diseases. However, the association between pemphigus and schizophrenia has not been established yet. We aimed to estimate the association between pemphigus and schizophrenia using a large-scale real-life computerised database.

Methods. This study was conducted as a cross-sectional study utilising the database of Clalit Health Services. The proportion of schizophrenia was compared between patients diagnosed with pemphigus and age-, gender- and ethnicity-matched control subjects. Univariate analysis was performed using χ^2 and Student's *t*-test and a multivariate analysis was performed using a logistic regression model.

Results. A total of 1985 pemphigus patients and 9874 controls were included in the study. The prevalence of schizophrenia was greater in patients with pemphigus as compared to the control group (2.0% *v.* 1.3%, respectively; $p = 0.019$). In a multivariate analysis, pemphigus was significantly associated with schizophrenia (OR, 1.5; 95% CI, 1.1–2.2). The association was more prominent among females, patients older than 60 years, and Jews.

Conclusions. Pemphigus is significantly associated with schizophrenia. Physicians treating patients with pemphigus should be aware of this possible association. Patients with pemphigus should be carefully assessed for comorbid schizophrenia and be treated appropriately.

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Key words: Association, cross-sectional, immunological hypothesis, pemphigus, schizophrenia.

Introduction

Pemphigus is a rare but life-threatening autoimmune bullous disease of the skin and mucous membranes, mediated by autoantibodies directed against desmosomal adhesion proteins (in particular, desmogleins 1 and 3) responsible for maintaining the integrity of the epidermis (Bystryn & Rudolph, 2005).

Pemphigus typically presents with mucosal ulcerations and superficial blisters and erosions affecting the trunk, face, scalp and proximal limbs. Since the blister forms within the epidermis, it is fragile and breaks easily. Mucosal lesions mainly involve the oral cavity, but can also spread to affect the larynx, pharynx, oesophagus, eyes and genitalia (Groves, 2009). Mortality due to pemphigus was dramatically reduced from 75% to 5–30% (Bystryn & Steinman, 1996; Uzun *et al.* 2006; Risser *et al.* 2009) since the introduction of corticosteroid treatment in the early 1950s. Morbidity as a consequence of therapy is now more common than mortality related to the underlying disease (Kridin *et al.* 2017).

Pemphigus is a relapsing, difficult-to-treat illness requiring long-term hospitalisation and immunosuppressive treatment. As it also affects the patient's appearance, it may inflict significant psychological trauma. Patients with pemphigus experience a major decrease in their quality of life, affecting physical, psychological and social aspects (Mayrshofer *et al.* 2005; Terrab *et al.* 2005; Tabolli *et al.* 2008; Paradisi *et al.* 2009; Sung *et al.* 2015).

Although psychodermatological research on pemphigus is relatively sparse, anxiety and depression have been reported to correlate with disease activity

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(Tabolli *et al.* 2008) and to persist during quiescent periods (Tabolli *et al.* 2014). A previous study performed by our group has shown an increased prevalence of comorbid depression among patients with pemphigus relative to matched control subjects (Wohl *et al.* 2015). In a recent Indian study of 50 pemphigus patients, psychiatric comorbidity was diagnosed in 26% of the patients (according to ICD-10) and in 40% of the patients (according to GHQ-12) (Kumar *et al.* 2013). A recent Iranian study using GHQ-28 bimodal scores reported a 73.7% prevalence of mental disorders among patients with pemphigus (Arbabi *et al.* 2011).

Immunological hypotheses have become increasingly prominent in psychiatric research (Müller & Schwarz, 2010), suggesting that autoimmunity may be involved in the etiopathogenesis of some patients with symptoms of schizophrenia (Drexhage *et al.* 2011; Benrós & Mortensen, 2015). Large-scale population-based epidemiological studies have shown that individuals with schizophrenia have a nearly 50% higher lifetime prevalence of autoimmune disorders (Eaton *et al.* 2006; Benros *et al.* 2011). Moreover, schizophrenia was found to be associated with a wide range of autoimmune and immune-related diseases, including Celiac disease, Graves' disease, psoriasis, pernicious anaemia, and hypersensitivity vasculitis (Chen *et al.* 2012). However, the epidemiological association between pemphigus and schizophrenia has not yet been examined.

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

Methods

Study design and database

The study was designed as a retrospective, population-based, cross-sectional study. Data-mining techniques were utilised to access information from the Clalit Health Services (CHS) database. CHS is the largest managed care organisation in Israel, serving a population of approximately 4 400 000 in 2016. CHS has a comprehensive computerised database with continuous real-time input from pharmaceutical, medical and administrative operating systems that facilitates gathering data for epidemiological studies. The validity of diagnoses in this registry, which are based on reports from hospital and primary care physicians and specialists, has been shown to be reliable (Rennert & Peterburg, 2001). The CHS database undergoes a continuous validation process by logistical checks (such as comparing the diagnoses from various sources) and by direct validation of the diagnoses by each patient's treating physician.

Study population and covariate factors

Patients were defined as having pemphigus when there was either a diagnosis of pemphigus documented at least twice in the medical records by a physician in the community or when pemphigus was listed in the diagnoses of a hospital discharge letter. Up to five control patients were randomly selected for each case patient. After excluding patients with pemphigus from the list of CHS members, the control group was randomly selected and matched to cases based on age, sex and ethnicity. Age matching was based on the exact year of birth (1-year strata). Controls were confirmed to be alive and to be contributing data to CHS on the date of the diagnosis of the matched case. This date of 'pseudodiagnosis' was assigned to each control subject and indicated the date of diagnosis of the matched case.

Data available from the CHS database included age, sex, socioeconomic status (SES), and diagnoses of chronic diseases. These diagnoses were extracted from the CHS registry of chronic diseases, which is based on data from hospital and primary care physicians' reports and validated by primary physicians. A Charlson comorbidity score was calculated for each of the study participants (Charlson *et al.* 1987). Healthcare utilisation was determined by the number of total visits per individual in the year before the diagnosis of pemphigus in cases and before 'pseudodiagnosis' in controls.

Statistical analysis

The distribution of sociodemographic and clinical factors between cases and control subjects was compared using χ^2 test for sex and SES and using *t*-test for age. Logistic regression was then used to calculate odds ratio (OR) and 95% confidence interval (CI) to compare schizophrenia between cases and controls. Homogeneity of ORs across strata was tested using Breslow–Day and Tarone's tests. The exact age matching permitted the use of unconditional logistic regression (Pearce, 2016).

Outcome measures were adjusted for comorbidities as determined by Charlson scores. To ensure that observed associations were not merely due to increased ascertainment, outcome measures were also adjusted for overutilisation of health services.

All statistical analysis was performed using SPSS software, version 18 (SPSS, Chicago, IL, USA).

Results

The study consisted of 1985 patients with pemphigus and 9874 age-, gender- and ethnicity-matched control subjects. The mean (±S.D.) age at presentation of pemphigus was 72.1 ± 18.5, which is identical to the age of control subjects at the date of their enrolment. 797

(40.2%) cases were male, with a similar proportion seen in controls. The ethnic and socioeconomic structure of the two groups was similar. While the prevalence of drug and alcohol abuse was comparable in the two groups, there was a higher proportion of smokers among control subjects. Comorbidity rates as measured by the Charlson index were higher in cases, with 1059 (53.4%) having severe comorbidity compared with 4055 (41.1%) in controls. Healthcare utilisation rates were lower in cases than controls; 65% of cases and 71% of controls had more than 12 consultations in the year prior to pemphigus diagnosis (Table 1).

The prevalence rate of schizophrenia was greater in patients with pemphigus than in control subjects (2.0% *v.* 1.3%, respectively; OR, 1.5; 95% CI, 1.1–2.2; $p = 0.019$). When stratified by age, the association was prominent for patients older than 60 years of age. A significant association was also seen among females and 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 schizophrenia was noted by any covariate (data not shown).

After controlling for confounders such as age, sex, ethnicity, SES, drug abuse, alcohol abuse, healthcare utilisation and comorbidities, pemphigus demonstrated a substantial independent association with schizophrenia in multivariable logistic regression analysis (OR, 1.6; 95% CI, 1.1–2.3; Table 3). Younger age, Jewish ethnicity, intermediate SES and drug abuse were also found to be associated with schizophrenia (Table 3).

Discussion

This is the first population-based study aiming to investigate the association between pemphigus and schizophrenia in a large cohort of pemphigus patients. Our findings revealed a significant association between pemphigus and schizophrenia with a multivariate OR of 1.6 (95% CI 1.1–2.3). The prevalence rate of schizophrenia in patients with pemphigus is remarkably higher than in age-, gender- and ethnicity-matched control subjects (2.0% *v.* 1.3%, respectively; $p = 0.019$).

Table 1. *Baseline characteristics of the study population*

Characteristic	Patients with pemphigus (N = 1985)	Controls (N = 9874)	p value
Age, years			
Mean ± S.D.	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%)	3962 (40.1%)	NS
Ethnicity, *N* (%)			
Jews	1805 (90.9%)	8866 (89.8%)	NS
Arabs	180 (9.1%)	1008 (10.2%)	
SES, *N* (%)			
Low	634 (31.9%)	3249 (32.9%)	NS
Intermediate	830 (41.8%)	4263 (43.2%)	NS
High	423 (21.3%)	2217 (22.5%)	NS
BMI, kg/m^2 (mean ± S.D.)	27.7 ± 6.6	27.9 ± 6.6	NS
Smoking, *N* (%)	510 (25.7%)	2758 (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%)	2636 (26.7%)	<0.001
Moderate (1–2)	582 (29.3%)	3183 (32.2%)	0.011
Severe (⩾3)	1059 (53.4%)	4055 (41.1%)	<0.001
Healthcare utilisation, *n* (%)			
0 visits	286 (14.4%)	770 (7.8%)	<0.001
1–12 visits	411 (20.7%)	2094 (21.2%)	NS
⩾13 visits	1288 (64.9%)	7010 (71.0%)	<0.001

OR, odds ratio; *n*, number; SES, socioeconomic status; CI, confidence interval; NS, non-significant; S.D., standard deviation; BMI, body mass index.

Table 2. *The association between pemphigus and schizophrenia stratified by age, gender, and ethnicity*

Subgroup	Number	Schizophrenia in patients with pemphigus ($N = 1985$) N (%)	Schizophrenia in controls ($N = 9874$) N (%)	OR (95% CI)	p value
All	11 859	39 (2.0%)	127 (1.3%)	**1.54 (1.07–2.21)**	**0.019**
Age, years					
0–39	872	0 (0.0%)	12 (1.6%)	ND	0.121
40–59	1768	3 (1.0%)	27 (1.8%)	0.55 (0.17–1.83)	NS
60–79	4121	20 (2.9%)	49 (1.4%)	**2.07 (1.22–3.51)**	**0.006**
⩾80	5098	16 (1.9%)	39 (0.9%)	**2.04 (1.14–3.68)**	**0.015**
Gender					
Male	4759	12 (1.5%)	57 (1.4%)	1.05 (0.56–1.96)	NS
Female	7100	27 (2.3%)	70 (1.2%)	**1.94 (1.24–3.04)**	**0.003**
Ethnicity					
Jews	10 671	38 (2.1%)	119 (1.3%)	**1.58 (1.09–2.29)**	**0.014**
Arabs	1188	1 (0.6%)	8 (0.8%)	0.70 (0.09–5.62)	NS

OR, odds ratio; *n*, number; CI, confidence interval; NS, non-significant.
Bold: significant value.

Psychiatric comorbidity in pemphigus

Psychiatric and psychological morbidity, such as anxiety, depression, obsessive-compulsive disorder and psychosis, is common and is reported in up to 30% of dermatologic disorders in all age groups (Gupta & Gupta, 2003; Wakkee & Nijsten, 2009; Al Hawsawi & Pope, 2011). The few studies that have investigated the presence of psychiatric comorbidity among patients with pemphigus have reported even higher prevalence rates of psychiatric comorbidities (Arbabi *et al.* 2011; Kumar *et al.* 2013). In the study of Kumar *et al.* (2013), 20 of 50 patients (40%) were screened GHQ-12 positive, including one patient who was diagnosed with acute and transient psychosis. Arbabi *et al.* (2011) found that 157 of 212 pemphigus patients scored ⩾6 on GHQ-28 bimodal scoring, indicating a 73.7% prevalence of comorbid mental disorder.

Table 3. *The association between pemphigus and schizophrenia after controlling for confounders by logistic regression model*

Variable	OR	95% CI	p value
Pemphigus	1.58	1.09–2.29	**0.017**
Age (per year)	0.98	0.98–0.99	**0.021**
Female sex	1.07	0.77–1.48	0.695
Jewish ethnicity (*v.* Arabs)	2.22	1.09–4.56	**0.029**
SES (low *v.* medium and high)	0.92	0.65–1.33	0.688
SES (low *v.* high)	1.59	0.79–2.57	0.080
SES (intermediate *v.* high)	2.04	1.28–3.23	**0.003**
Drug abuse	13.34	5.99–29.74	**<0.001**
Alcohol abuse	0.33	0.04–2.52	0.284
Healthcare utilisation	0.99	0.98–0.99	**0.008**
Charlson comorbidity score	1.05	0.97–1.13	0.229

CI, confidence interval; NS, non-significant; SES, socio-economic status.
Bold: significant values.

Autoimmune comorbidity in schizophrenia

Increased prevalence of autoimmune diseases has been observed among patients with schizophrenia relative to control subjects (Benrós & Mortensen, 2015). In addition, increased autoantibody titres, as well as autoantibody reactivity, were identified even in patients without overt clinical manifestation of autoimmune disease (Tanaka *et al.* 2003; Laske *et al.* 2008). Danish population-based studies of up to 20 317 patients with schizophrenia and 39 076 patients with non-affective psychosis have demonstrated that individuals with schizophrenia had an approximately 50% higher prevalence of autoimmune conditions (Eaton *et al.* 2006; Benros *et al.* 2011).

Screening studies of individuals with schizophrenia have observed a 500% higher seropositivity to tissue transglutaminase as compared with matched control subjects (Reichelt & Landmark, 1995; Samaroo *et al.* 2010; Cascella *et al.* 2011), suggesting a connection to the pathogenesis of celiac disease. Observational studies have estimated the prevalence of celiac disease to range between 2.1% and 2.6% among patients with schizophrenia, as compared with a prevalence between 0.3% and 1.0% seen in the general population (Kalaydjian *et al.* 2006; Cascella *et al.* 2011). In a cross-sectional national Taiwanese study, 3.4% of individuals with a hospital

contact for autoimmune diseases also had a hospital contact with schizophrenia during the follow-up period (Chen *et al.* 2012). According to Danish registry data, hospital contacts due to autoimmune diseases had occurred in 2.4% of patients before a schizophrenia diagnosis and in 3.6% of patients after the diagnosis, indicating that 6% of people with schizophrenia had a hospital contact with autoimmune diseases during the study duration (Benros *et al.* 2011, 2014).

Explanation for the observed association between pemphigus and schizophrenia

The pathophysiological mechanism-linking schizophrenia with autoimmune comorbidities has not yet been fully elucidated. It has been suggested that the psychiatric symptoms in patients with autoimmune comorbidities can be triggered by the direct effect of immune factors, such as brain-reactive autoantibodies and cytokines, on the central nervous system (CNS) or be secondary to systemic inflammation indirectly affecting the brain (Benrós & Mortensen, 2015).

With regard to the direct effect of immune components, experimental studies have found that neuropsychiatric syndromes can be induced after the influx of brain-reactive antibodies into the brain (Kowal *et al.* 2004). Brain-reactive autoantibodies have also been suspected to induce the high prevalence of neuropsychiatric symptoms encountered in some autoimmune disease (Margutti *et al.* 2006; Ballok, 2007; Sundquist *et al.* 2008). This is of great relevance in a B-cell-mediated disease like pemphigus, where autoantibodies are necessary for the stimulation of the disease. In addition, one of the target autoantigens implicated in the pathogenesis of pemphigus, desmoglein-1, was recently found to be expressed in the corpus callosum of mouse models (Miyata *et al.* 2015). Given that desmoglein-1 is expressed both in the epithelial cell surface and in the CNS (Kljuic & Christiano, 2003; Miyata *et al.* 2015), the hypothesis of cross-reactivity between its epithelial and neuronal isoforms and the production of brain-reactive autoantibodies as a reason for the higher prevalence of schizophrenia in pemphigus patients cannot be thoroughly excluded. The most representative model for CNS symptoms associated with antibodies has been recognised in cancer patients with paraneoplastic symptoms that may in part be induced by the cross-reaction between antibodies against tumour antigens with elements of the nervous system (Darnell & Posner, 2003; Kayser *et al.* 2010). The inflammatory state existing in autoimmune diseases, and in pemphigus in particular, might increase the permeability of the blood–brain barrier, making the brain more vulnerable to these autoantibodies and inflammatory cytokines (Irani & Lang, 2008).

The indirect contribution of systemic inflammation accompanying autoimmune diseases in triggering neuropsychiatric symptoms may be mediated by the interaction with the neuroendocrine system, which is thought to play an important role in psychiatric disorders through multiple pathways (Dantzer *et al.* 2008; Rivest, 2010). An iatrogenic effect of corticosteroid treatment, which may hypothetically increase the risk of psychosis, seems unlikely to explain the major associations (Benrós & Mortensen, 2015). Separate research shows a reduced risk for psychosis observed with the use of corticosteroids(Laan *et al.* 2009) and newer biological treatment of autoimmune diseases has been shown to decrease the risk of mood disorders (Benrós & Mortensen, 2015). In addition, antipsychotic treatments were very rarely associated with the induction of pemphigus (Pérez España *et al.* 2003).

The associations in our population could also be caused by a shared genetic predisposition, as both pemphigus and schizophrenia are more frequent among patients of Ashkenazi Jewish ancestry (Lencz *et al.* 2013; Kridin *et al.* 2016). Although the association seems biologically plausible, it remains widely unclear whether it is a causal association or an epiphenomenon due to, for instance, other environmental factors. The cross-sectional nature of the current study does not enable to address the temporal relationship between the two entities; hence, limited conclusions should be drawn regarding a causal association between the entities (Höfler, 2005).

Strengths and limitations

Our population-based study utilises a representative database, created over 11 years, of 4.4 million individuals, decreasing the susceptibility to selection and ascertainment biases. Data collection in pemphigus is difficult due to disease rarity and the limited number of patients available for study. This lack of large-scale clinical data is a significant impediment to a better understanding of the disease associations and comorbidities. Our study includes one of the largest cohorts of patients with pemphigus reported in the literature and is the first study aiming to examine the association between pemphigus and schizophrenia.

The study has several considerable limitations. Firstly, the study lacks clinical data concerning pemphigus subtype (vulgaris, foliaceus or paraneoplastic), clinical characteristics and severity. Secondly, since the data extracted from the database represents only a current situational analysis of co-existing variables without regard to chronology, the date of schizophrenia diagnosis was not available for the current study.

Hence, we could not address temporal relationships between pemphigus and schizophrenia; limited conclusions should be drawn regarding a causal association between the two entities (Höfler, 2005). Additionally, the use of routinely-collected 'real-life' data did not enable direct validation of diagnoses nor did it allow for the elimination of cases of misclassification. However, if misclassification did occur, it would be non-differential and might lead to a null bias. Pemphigus in Israel is uncommonly encountered in general practice. Diagnosis relies on skin biopsies, as well as direct and indirect immunofluorescence (Kridin *et al.* 2016) usually carried out in secondary and tertiary care facilities; therefore, it is very likely to be precise and validated. Furthermore, the diagnosis of schizophrenia is performed by trained psychiatrists, who are the only practitioners legally allowed in Israel to treat patients with psychiatric disorders. The existence of ascertainment bias was ruled out when our outcome measures were reproduced after adjusting for overutilisation of healthcare services.

Conclusions

In conclusion, our population-based study depicts a significant association between pemphigus and schizophrenia. It appears that the highest increase in schizophrenia burden among pemphigus patients occurs in older Jewish females. Patients with pemphigus should be carefully assessed for comorbid psychiatric disorders and be treated appropriately. Experimental research is needed to better understand the molecular mechanisms behind this novel observation.

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Conflict of Interest

The authors declare no conflict of interests.

Ethical Standard

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Availability of Data and Materials

The full row data will not be shared as we have no ethical permission to perform this.

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