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Increased risk of depression in patients with cutaneous lupus erythematosus and systemic lupus erythematosus: a Danish nationwide cohort study

Running head: Increased risk of depression in patients with lupus erythematosus

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Conflicts of interest

A. Egeberg has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals.

G. Gislason, J. H. Hesselvig, K. Kofoed, and L. Dreyer have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

What's already known about this topic?

- Reported prevalences of depression in patients with systemic lupus erythematosus range widely, while the prevalence of depression in cutaneous lupus erythematosus remains severely understudied.

What does this study add?

- In this nationwide cohort study patients with cutaneous or systemic lupus erythematosus had a 2-fold increased risk of depression compared with the general population in Denmark.
- The risk of self-harm and death from suicide were not significantly increased in patients with lupus erythematosus.

Summary

Background Reported prevalences of depression in patients with systemic lupus erythematosus (SLE) range widely, while the prevalence of depression in cutaneous lupus erythematosus (CLE) remains severely understudied.

Objectives To examine whether patients with SLE or CLE have increased risk of depression.

Methods In this nationwide observational cohort study, we included patients ≥ 18 years with a first-time diagnosis of SLE or CLE between 2000–2015 identified in the Danish National Patient Register matched with general population in a 1:10 ratio. After linkage to national Danish health registers of primary and secondary care, analyses of risk for depression and antidepressant use were performed in Cox regression models adjusted for age, sex, socio-economic status, smoking, alcohol abuse, prior depression, and prior antidepressant use.

Results A total of 3,489 patients with lupus erythematosus were followed for 23,373 person-years. The adjusted hazard ratios (HRs) of depression were 2.07 (95% CI, 1.55–2.75) and 2.22 (95% CI, 1.77–2.77) for patients with CLE and SLE, respectively, compared with general population; for hospitalization due to depression at department of Psychiatry, HRs were 2.63 (95% CI, 0.80–8.67) and 3.52 (95% CI, 1.53–8.11) for patients with CLE and SLE, respectively. The adjusted HRs of antidepressant use were 1.47 (95% CI, 1.34–1.63) and 1.70 (95% CI, 1.58–1.83) for patients with CLE and SLE.

Conclusions The risk of depression was significantly increased in patients with SLE and CLE. Awareness of increased risk of depression in patients with SLE and CLE might be warranted.

Introduction

Lupus erythematosus (LE) is a chronic autoimmune disease which may present in a systemic or a localized cutaneous form. As apparent by the name systemic lupus erythematosus (SLE) may not only involve the skin but also internal organs such as lungs, heart, and kidneys, whereas cutaneous lupus erythematosus (CLE) is mainly restricted to the skin[1].

Quality of life is considerably impaired in patients with SLE as well as in patients with CLE[2,3]. In patients with SLE, prevalence of depression ranges from 2–92% depending on factors such as study design and diagnostic criteria[4], while the prevalence of depression in CLE remains severely understudied. Likewise, data on the incidence of depression in adults after being diagnosed with CLE or SLE remain scarce.

Since depression is associated with morbidity, decreased quality of life, and increased mortality for the individual patient[5,6] as well as a high economic burden on society[7], it is important to investigate whether patients with CLE or SLE have an increased risk of depression. We therefore investigated the association between LE and risk of depression in a nationwide cohort of the Danish population.

Materials and methods

Study design

A nationwide longitudinal cohort study was performed to examine whether patients with SLE or CLE have increased risk of depression.

Data sources

To conduct the current study nationwide Danish health registers were used. In Denmark, each resident is given a unique and lifelong Civil Personal Register (CPR) number at birth or upon immigration to Denmark. This CPR number makes it possible to cross-link between a wide range of national health registers.

From the Danish Civil Registration System, information on date of birth, sex, migration, ethnicity, and vital status were obtained[8]. Diagnoses were acquired from the Danish National Patient Register (DNPR). The Danish National Health Service Register (NHSR) contains information from the primary care and is a part of the tax-funded public healthcare system[9]. Data were also obtained from the Register of Medicinal Products Statistics that contains information on all pharmacy-dispensed and redeemed prescription since 1995[10]. The data regarding suicides were obtained from the Register of Causes of Death[11]. Finally, information on socio-economic status was calculated based on data from the Income Statistics Register[12]. See Supplementary File for elaborating description of data sources.

Study population

The source population comprised all residents in Denmark ≥ 18 years from 2000–2015. People < 18 years were included the subsequent day of their 18th birthday.

We identified all patients with a first-time diagnosis of CLE or SLE, either as primary or supplementary diagnosis (Supplementary Table I). Patients with a diagnosis of CLE or SLE before baseline were excluded. The baseline or index date for CLE or SLE was the date of the first diagnosis, and each case was matched on age, sex, and index date in a 1:10 ratio with individuals from the general population serving as reference group. That the reference group was matched on the index data meant that, i.e. patients in the reference population had to be alive, resident in the source population, and at risk of developing SLE or CLE at the date of the SLE/CLE diagnosis for the corresponding case. The index date for the matched population was the index date for the corresponding cases. The study population was followed from 1 January 2000 until 31 December 2015, emigration, death, or the occurrence of an endpoint, whichever occurred first. Patients were matched with a reference population on age and sex.

Covariates

A proxy for smoking was assessed using data on drugs prescribed for smoking cessation, diagnoses of smoking, tobacco use, chronic obstructive pulmonary disease, lung cancer, or treatments and/or therapeutic interventions aimed at smoking cessation[13].

Alcohol abuse was assessed by diagnoses of alcohol abuse or conditions strongly related to alcohol abuse, pharmacological treatment with drugs used for alcohol dependence, and treatment interventions for alcohol dependence[14].

Socio-economic status was defined by the average household income in the 5 years preceding index and was divided into age-standardized quintiles.

Baseline depression was defined as a diagnosis of depression up to 5 years prior to index.

Outcomes

The primary study endpoint was depression, defined by either a diagnosis of depression recorded in the DNPR (ICD-10 codes F32 or F33) or depression registered by psychologists or GPs in the NHSR (Supplementary Table I). At the GP, the registration was the use of Hamilton Rating Scale for Depression, which is a test used to assess the severity of the depression. At the psychologist, the registration was a consultation due to depression.

The secondary endpoint was a claimed prescription for antidepressants.

Statistical analysis

Continuous variables were presented as mean with standard deviation if normally distributed or as median with interquartile range if distribution was skewed, and frequencies with percentages for categorical data.

Incidence rates (IRs) of depression and antidepressant use were determined for CLE, SLE, and general population and expressed as the number of events per 1,000 person-years (PY). Analyses of depression risk were performed in Cox regression models using calendar time as time scale and adjusted for sex, age, smoking, alcohol abuse, socio-economic status, previous depression, and prior antidepressant use. The variable, ethnicity, was not significant in univariate analysis and thus not included in the adjusted Cox regression model. Smoking, alcohol abuse, sex, previous depression,

and prior antidepressant use were all handled as binary variables in the analysis, whereas age was handled as a continuous variable, and socio-economic status as a categorical variable. Smoking, alcohol abuse, and LE status were included as time-dependent variables. LE status as time-dependent variable made it possible to change status from CLE to SLE but not the opposite way. Model assumptions, including the proportional hazards assumption was tested and found to be valid.

Due to clinical relevance, we performed subgroup analyses by sex, age (< 50 years, ≥ 50 years at LE diagnosis), and severe depression, which was defined as patients hospitalized due to depression at a hospital in general or at a department of Psychiatry.

We considered a 2-sided p-value < 0.05 as statistically significant. Data management and statistical analyses were performed with the use of SAS software version 9.4 (SAS Institute, Cary, NC, USA) and Stata/MP version 14 (StataCorp, College Station, TX, USA).

Sensitivity analyses

First, we limited our inclusion to patients with a CLE or SLE diagnosis made by a rheumatologist, dermatologist or nephrologist to be surer of an accurate diagnosis. Second, to increase the validity of the definition of SLE we identified patients with SLE in two different ways; in one sensitivity analysis by using a previous validated algorithm for SLE with a positive predictive value (PPV) of 89%[15], and in another by only including patients with SLE on systemic therapies as methotrexate, hydroxychloroquine and systemic corticosteroids during follow-up.

Furthermore, we made a sensitivity analysis excluding patients diagnosed with depression within 3 months of their first LE diagnosis to give an impression if depression is a neuropsychiatric manifestation at time of LE or if depression is more prominent as a long-term outcome of LE. We also made an analysis where we excluded patients with prior depression (defined as 5 years before index) and prior antidepressant use (defined as 12 months before index), respectively. Additionally, we made a sensitivity analysis where we used LE status as a fixed variable. Patients with a diagnosis of both CLE and SLE were in a separate group. To address surveillance bias, we made a sensitivity analysis with an outcome which we did not believe was associated with LE. Our outcome was azithromycin, only azithromycin used for treatment of chlamydia (defined as 1 g of azithromycin in a single dose).

Results

The study comprised 1,424 and 2,065 patients with CLE and SLE, respectively, matched with 34,890 people from the general population in Denmark.

Baseline characteristics of our study population are shown in Table 1. Overall, the median age for the first diagnosis of CLE or SLE at the hospital was approximately 51 years, however, patients with CLE being slightly older. More patients with LE smoked and had alcohol abuse compared with general population.

The number of patients diagnosed with depression were 51, 89, and 653 in CLE, SLE, and general population, respectively. For depression, the follow-up time were 8,103, 15,270, and 253,547 PY for CLE, SLE, and general population, respectively, and the corresponding IRs were 6.29 (95% CI, 4.78–8.28), 5.83 (95% CI, 4.74–7.17), and 2.58 (95% CI, 2.24–2.78) per 1,000 PY.

The number of patients using antidepressants were 419, 790, and 8,224 in CLE, SLE, and general population, respectively. For antidepressant use, the follow-up time were 6,222, 11,074, and 212,148 PY for CLE, SLE, and general population, respectively, and the corresponding IRs were 67.34 (95% CI, 61.19–74.10), 71.34 (95% CI, 66.53–76.49), and 38.77 (95% CI, 37.94–39.61) per 1,000 PY.

The period prevalence of depression corresponding to the study period was 3.6% in CLE, 3.4% in SLE, and 1.9% in the general population. The same pattern was observed for antidepressant use with period prevalences at 29.4%, 31.9%, and 23.6% in CLE, SLE, and in the general population, respectively.

The use of hydroxychloroquine, methotrexate, systemic corticosteroids, and topical corticosteroids increased during follow up compared with baseline use (data not shown). However, only 50.1% and 46.5% with CLE and SLE were treated with hydroxychloroquine during follow-up.

Diagnoses of LE were associated with a significantly increased risk of depression. When adjusting for age, sex, smoking, alcohol abuse, socio-economic status, prior depression, and prior antidepressant use the HRs were 2.07 (95% CI, 1.55–2.75) and 2.22 (95% CI, 1.77–2.77) for patients with CLE and SLE, respectively (Table 2).

In a subgroup analysis, we found that patients with LE had an increased risk of severe depression compared with general population. For patients hospitalized due to depression at a hospital in general, the adjusted HRs were 2.90 (95% CI, 1.32–6.36) and 2.60 (95% CI, 1.32–5.06) for CLE and SLE, respectively. However, for patients hospitalized due to depression at a department of Psychiatry, the adjusted HRs were 2.63 (95% CI, 0.80–8.67) and 3.52 (95% CI, 1.53–8.11) for CLE and SLE, respectively (Supplementary Table II).

Likewise, a significant association was seen between LE and antidepressant use. The adjusted HRs were 1.47 (95% CI, 1.34–1.63) and 1.70 (95% CI, 1.58–1.83) for patients with CLE and SLE, respectively (Table 2). HR for each covariate is presented in Supplementary Table III.

The risk of depression was more pronounced in patients diagnosed with CLE or SLE < 50 years of age, especially for CLE. The adjusted HRs were 3.15 (95% CI, 2.02–4.92) and 2.28 (95% CI, 1.60–3.25) for patients with CLE and SLE < 50 years of age. For antidepressant use, the stratification in age did not alter the results significantly (Table 2).

When stratifying for sex, the risk of depression or antidepressant use was significantly increased for both men and women. Men with CLE had a higher risk of depression than women. For antidepressant use, men with SLE had the highest risk (Supplementary Table IV).

In a post hoc analysis, we found that death from suicide in general was seldom: only 3 completed suicides in the LE group and 43 completed suicides in the general population. The crude HR was 0.72 (95% CI, 0.22–2.31) with p-value 0.576 and the adjusted HR was 0.55 (95% CI, 0.17–1.78) with p-value 0.316 for completed suicides in patients with LE overall compared with general population. Likewise, self-harm were seldom with 3 and 31 cases in the LE group and general population. The crude HR for self-harm in the LE group compared with general population was 1.00 (95% CI, 0.30–3.26) with p-value 0.995 and the adjusted HR was 0.78 (95% CI, 0.24–2.58) with p-value 0.689.

Sensitivity analyses

We excluded patients with prior depression or prior antidepressant use from the analyses, which did not alter the clear trends in the study results (Supplementary Table V). Neither did the results alter worthily or significantly when we excluded patients diagnosed with depression within 3 months of their first LE diagnosis (data not shown). When using a previously validated algorithm[15] for defining patients with SLE, we found that the adjusted HRs were 2.04 (95% CI, 1.31–3.19) for depression and

1.56 (95% CI, 1.36–1.79) for antidepressant use (Supplementary Table VI). When we only included patients with SLE on systemic therapies as methotrexate, hydroxychloroquine and systemic corticosteroids during follow-up, we found that the statistical significance retained, the adjusted HRs were 2.48 (95% CI, 1.87-3.30) with a p-value <0.0001 for depression and 1.78 (95% CI, 1.63-1.94) with a p-value <0.0001 for antidepressant use. In the sensitivity analysis in which we only included patients with CLE or SLE diagnosed from a department of rheumatology, dermatology or nephrology, the results did not alter worthily (Supplementary Table VII). In the sensitivity analysis with CLE and SLE status as fixed variables the results were not significantly altered (Supplementary Table VIII). Finally, in the sensitivity analysis where the outcome was treatment with azithromycin for chlamydia, we found a crude HR of 1.31 (95% CI, 1.04–1.65) and an adjusted HR of 1.17 (95% CI, 0.93–1.48) for patients with LE compared with general population.

Discussion

In this nationwide cohort study to examine the risk of depression in patients with LE, we found a 2-fold increased risk of depression in patients with CLE or SLE compared with a matched group from the general population in Denmark. The risk for depression was of similar magnitude in the two groups, which indicates that the involvement of the skin has the same important impact as the systemic disease.

The cause for the increased risk of depression in patients with SLE remains unclear. It is probably due to both direct and indirect consequences of the disease; a directly consequence as due to the systemic inflammation, and an indirectly consequence as due to the psychological burden of having and coping with a chronic disease[16–20]. Previous studies have shown that depression is associated with inflammation. Proinflammatory cytokine levels such as interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α are increased in patients with depression[16,17]. A study has shown that sera TNF-α levels are increased in patients with SLE and concomitant depressive symptoms[19]. However, a systematic review found that psychological factors were the most frequently reported cause for the association between SLE and depression[18]. The association between an autoimmune disease and a neuropsychiatric disease is also found in other autoimmune diseases beside LE, e.g. in patients with rheumatoid arthritis[21,22].

In general, patients with dermatologic diseases have a reduced quality of life and have an increased prevalence of psychiatric morbidity including depression[2]. This is shown in previous studies where an association between depression and atopic dermatitis[23], rosacea[24], and psoriasis[25] is found, which is in line with our findings regarding CLE and the increased risk of depression and antidepressant use.

A systematic review and meta-analysis from 2017 with 59 studies reporting on a total of 10,828 patients with SLE found that the prevalence of depression ranged from 2–92% between the studies [4]. This diversity is due to variation in the study design, sample size, country, and different definitions of depression. The meta-analysis showed that the pooled prevalence of depression in patients with SLE was 24% (95% CI, 16-31%) when using the Diagnostic and Statistical Manual of Mental Disorders and/or ICD diagnostic criteria[4]. This prevalence is higher than our period prevalence of depression, 3.4%, and slightly lower than our period prevalence for antidepressant use, 31.9%. This indicate that the "true" prevalence of depression is somewhere between these prevalences. The reason for the discrepancy could be that we find too few patients with depression (see under *Limitations and strengths*) and only the severe cases with depression (patients seen at a hospital, seen by a psychologist or having a Hamilton Rating Scale for Depression test done at the GP).

In contrast to SLE, the general knowledge regarding the association of patients with CLE and depression is sparse. Only one previous study with a small sample size has examined the prevalence and odds ratio (OR) of depression in patients with CLE[26]. This study showed a point prevalence of 9% for depression, a lifetime prevalence of 44%, and an OR 2.5 (95%, CI 1.2-5.0) for lifetime depression in patients with CLE[26].

The suicide risk is increased in patients with depression[6]. In our study the number of attempts and completed suicides was low and not increased in patients with LE compared with general population. Previous studies have described that suicidal ideation is common in SLE and, likewise, that the incidence rates of completed suicides and attempts are increased[27,28].

Limitations and strengths

Several limitations need to be addressed. One limitation of the study is that some patients with CLE are followed by their private dermatologist or GP. Thus our results cannot be generalized to these patients who probably have a less severe disease burden and a lower risk of depression than patients followed in hospitals. Conversely, patients with SLE are typically followed at the hospital[29].

Another limitation is the risk of not including all patients with depression. Firstly, far from all patients with depression are seen at a hospital. Secondly, there is a possibility that not all GP use the Hamilton Rating Scale for Depression to assess the severity of the depression, even though they are charged for it. This will underestimate the risk of depression in all groups. On the other hand, patients with LE receive increased medical scrutiny compared to general population, potentially giving rise to surveillance bias, i.e. increased contact with healthcare professionals increasing the likelihood of being diagnosed with depression. However, thirdly, fatigue and other symptoms of mood disorders are common in patients with SLE, thus patients' complaints might be classified as symptom of SLE and not a depression. In the current study, we did not include the *ICD-10 depression test* or *psychometric test for depression*, as this would overestimate the risk of depression in each group, as not everyone who takes the test will be diagnosed with depression. The use of antidepressants as a surrogate marker of depression is not accurate as some patients treated with antidepressants are treated for anxiety, sleeping disorder or obsessive-compulsive disorder[30]. A study showed that the main indication in Denmark for treatment with antidepressant was depression followed by anxiety[31].

The strengths of our study are the nationwide covered registers with virtually complete follow-up, which was conducted in a country with free healthcare. Likewise, the long follow-up period and the large number of patients represent major strengths. To our knowledge, we are the first to examine the risk of depression in patients with SLE compared to a general population. We attempted to adjust for important confounders such as smoking and alcohol abuse by using proxies. However, the use of these proxies may result in residual confounding. Further, we made numerous sensitivity analyses, including a validated algorithm to identify patients with SLE, and none of them did alter the results significantly. Likewise, we made a sensitivity analysis with azithromycin as outcome where the magnitude of the HR suggests slight surveillance bias, however unlikely to fully explain our results. Due to the observational study design, we cannot conclude anything on causality, even though the sensitivity analysis excluding patients diagnosed with depression within 3 months of their first LE diagnosis gives the impression that depression is a long-term outcome of the LE disease, or at least it is less convincing that depression is due to a neuropsychiatric manifestation at time of LE diagnosis.

We found significantly increased risk of depression in patients with CLE and SLE compared with a matched group from the general population in Denmark. The risk for depression is of similar magnitude in both groups indicating that the involvement of the skin as well as the systemic involvement affects the overall risk of depression. Notably, rheumatologists and dermatologists should be aware of the increased risk of depression in patients with LE.

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Table 1 Baseline characteristics of the study population

Characteristics	Patients with lupus erythematosus* (n = 3,489)		General population
	CLE (n = 1,424)	**SLE** (n = 2,065)	(n = 34,890)
Age (years), median (IQR)	54.3 (41.8, 66.2)	48.9 (35.6, 61,8)	51.1 (38.0, 63.8)
Women, n (%)	1,127 (79.1)	1,660 (80.4)	27,870 (79.9)
Smoking, n (%)	402 (28.2)	504 (24.4)	5,213 (14.9)
Socio-economic status, n (%)			
Lowest	244 (17.1)	400 (19.4)	7,031 (20.2)
Below average	372 (26.1)	439 (21.3)	6,865 (19.7)
Average	309 (21.7)	457 (22.1)	6,910 (19.8)
Above average	268 (18.8)	385 (18.6)	7,023 (20.1)
Highest	231 (16.2)	384 (18.6)	7,061 (20.2)
Ethnicity, n (%)[a]			
Ethnic Danes	1,331 (93.5)	1,916 (92.8)	32,856 (94.2)
Immigrants	88 (6.2)	138 (6.7)	1,858 (5.3)
Descendants	5 (0.4)	11 (0.5)	175 (0.5)
Comorbidity, n (%)			
Alcohol abuse	114 (8.0)	95 (4.6)	1,299 (3.7)
Depression[b]	21 (1.5)	37 (1.8)	279 (0.8)
Medication, n (%)[c]			
Antidepressants	36 (2.5)	80 (3.9)	565 (1.6)
Hydroxychloroquine	142 (10.0)	114 (5.5)	11 (0.03)
Methotrexate	17 (1.2)	62 (3.0)	59 (0.2)
Systemic corticosteroids	124 (8.7)	223 (10.8)	436 (1.3)
Topical corticosteroids	153 (10.7)	128 (6.2)	733 (2.1)

* Lupus erythematosus status is in this baseline table indicated as first-time registration of CLE or SLE, which only are for descriptive purposes. In the analyses, LE status is used as a time-dependent variable.

[a] Due to Denmark's Statistic, an immigrant is defined as a person not born in Denmark and none of the parents are Danish citizens or born in Denmark. Descendant is defined as a person born in Denmark, where none of the parents are Danish citizens or born in Denmark.

[b] Baseline depression is 5 years prior to index.

[c] Baseline medication is a claimed prescription up to 12 months prior to index.

CLE, cutaneous lupus erythematosus; IQR, interquartile range; SLE, systemic lupus erythematosus.

Table 2 Crude and adjusted hazard ratios for depression and antidepressant use in patients with lupus erythematosus compared with the general population, below stratified for age (< 50 years and ≥ 50 years at diagnosis of lupus erythematosus)

	Crude HR	(95% CI)	P-value	Adjusted HR*	(95% CI)	P-value
Depression						
CLE	2.53	(1.90-3.37)	<0.0001	2.07	(1.55-2.75)	<0.0001
SLE	2.38	(1.90-2.97)	<0.0001	2.22	(1.77-2.77)	<0.0001
Antidepressant use						
CLE	1.73	(1.56-1.90)	<0.0001	1.47	(1.34-1.63)	<0.0001
SLE	1.87	(1.74-2.02)	<0.0001	1.70	(1.58-1.83)	<0.0001

	Age < 50 years			Age ≥ 50 years		
	Adjusted HR*	(95% CI)	P-value	Adjusted HR*	(95% CI)	P-value
Depression						
CLE	3.15	(2.02-4.92)	<0.0001	1.72	(1.18-2.51)	0.005
SLE	2.28	(1.60-3.25)	<0.0001	2.12	(1.58-2.83)	<0.0001
Antidepressant use						
CLE	1.62	(1.38-1.89)	<0.0001	1.42	(1.25-1.62)	<0.0001
SLE	1.65	(1.38-1.89)	<0.0001	1.73	(1.56-1.92)	<0.0001

[a] Defined by either a diagnosis of depression recorded in the Danish National Patient Register or depression registered by psychologists or general practitioners in the Danish National Health Service Register.

CI, confidence interval; CLE, cutaneous lupus erythematosus; HR, Hazard Ratio; SLE, systemic lupus erythematosus.

* Adjusted for age, sex, smoking, alcohol abuse, socio-economic status, prior depression, and prior antidepressant use.