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Depression Risk in Young Adults with Childhood- and Adult-Onset Lupus: 12 Years of Follow-up

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Abstract

Objective—To compare major depression risk among young adults with childhood-onset and adult-onset systemic lupus erythematosus (SLE), and to determine demographic and health-related predictors of depression.

Methods—Young adults with SLE ages 18–45 years (n=546) in the Lupus Outcomes Study completed annual telephone surveys from 2002–2015, including assessment of depression using the Center for Epidemiological Studies Depression Scale (CES-D), and self-report measures of sociodemographics and health characteristics. Childhood-onset SLE (cSLE) was defined as age at diagnosis less than 18 years (N=115). Repeated measures analysis was performed to assess risk for major depression (CES-D≥24) at any point in study, and logistic regression was used to assess for recurrent (present on ≥2 assessments) major depression.

Results—Major depression was experienced by 47% of the cohort at least once during the 12-year study period. In adjusted analysis, cSLE patients had an increased risk of major depressive episode (OR 1.7, 95% CI 1.0–2.7) and recurrent episodes (OR 2.2, 95% CI 1.2–4.3), compared to participants with adult-onset SLE. Older age, lower educational attainment and physical function, higher disease activity, and history of smoking were associated with an increased depression risk. cSLE patients had a higher risk of major depression across all educational groups.

Conclusion—Young adults with SLE, particularly those with childhood-onset disease, are at high risk for major depression, which is associated with increased disease activity, poorer physical functioning, and lower educational attainment. Early depression intervention in young adults with SLE has the potential to improve both medical and psychosocial outcomes.

INTRODUCTION

Depression is a common comorbidity among patients with systemic lupus erythematosus (SLE). Affecting up to 60% of adults with SLE, depression is likely multifactorial in etiology(1), including central nervous system inflammation, the psychological burden of chronic disease, effects of steroid treatment, social, cultural and genetic factors. Depression is associated with adverse outcomes including poorer medication adherence, and higher

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healthcare utilization in individuals with SLE(2), making early recognition and intervention critical. Previous studies indicate that young adults with SLE have the highest risk of major depression among adults with SLE(3), which may create significant barriers to both disease management and psychosocial success.

Approximately 20% of patients with SLE have childhood onset disease (cSLE), which is often more severe than adult-onset SLE (aSLE) and may convey an increased risk for depression. Compared to those with aSLE, adults with cSLE have higher frequency of lupus nephritis, and greater requirement for high-dose prednisone and immunosuppressive therapies. Additionally, the psychological burden of disease may be magnified for individuals with cSLE, as the typical onset of cSLE occurs during adolescence, a critical time for psychosocial development and a peak time for onset of childhood depression(4). Pediatric patients with SLE have a higher prevalence of depressive symptoms at 20% compared to 8% in their healthy peers, and 13% in the general adolescent population(5); however, adult depression risk in patients with cSLE is unknown. As persistent depression symptoms in the general adolescent population have been associated with increased risk of major depression and suicide in adulthood(6), understanding the long-term risk and associated predictors of depression for patients with cSLE is necessary to optimize mental health intervention to improve their clinical and psychosocial outcomes.

We sought to determine the impact of childhood-onset disease and other factors on the longitudinal risk of depression in early adulthood. Specifically we aimed to: 1) compare the period prevalence of depression among young adults with cSLE and aSLE over 12 years, and 2) determine demographic and health-related predictors of depression in this population.

PATIENTS AND METHODS

Data Source

The study cohort consisted of 1281 individuals participating in the 2002–2015 interviews of the Lupus Outcomes Study (LOS), a prospective longitudinal cohort of adults with SLE from the U.S. Details regarding eligibility and enrollment are described elsewhere(7). Briefly, all participants had a confirmed diagnosis of SLE according to chart review supervised by a rheumatologist. Subjects participated in annual structured telephone interviews conducted by trained interviewers. The survey included validated items pertaining to demographic and socioeconomic characteristics, SLE manifestations, medications, general health, mental health, cognition, employment, and health care utilization. All study data were obtained by participant self-report. The study protocol was approved by the UCSF Committee on Human Research.

Measures

The primary outcome was the presence of high levels of depressive symptoms suggesting major depression at any point in the study. Depressive symptoms were assessed at each interview using the Center for Epidemiological Studies Depression Scale (CES-D), the measure suggested by the ACR Committee on Neuropsychiatric Lupus. A CES-D score of 24 or higher has been found to correspond to a diagnostic interview conclusion of major

depressive disorder in 94% of patients (sensitivity 88%, specificity 93%)(8). For brevity, we will refer to such high levels of depressive symptoms as major depression.

The primary predictor variable was cSLE, defined as age <18 years at diagnosis. Sociodemographic predictors included age, sex, race/ethnicity, education attained, marital status, employment and poverty. Subjects who reported currently working, currently having a job but not working, or having performed any work for pay or profit in the past week were considered employed, consistent with U.S. employment statistics (http://www.census.gov/cps). Poverty was defined as household income of less than 125% of the federal poverty level in the year prior to interview. SLE-associated predictors included disease duration, disease activity, current steroid use, current dialysis dependence and history of renal transplant. Disease activity was defined according to the Systemic Lupus Assessment Questionnaire (SLAQ), a validated self-report measure with possible scores ranging from 0 to 47(9). Current steroid use was defined as having received any oral or IV glucocorticoids in the past year. Self-report of renal outcomes has been validated in this cohort via chart review, with high agreement observed (kappa coefficient >0.80). General health predictors included physical function, body mass index, diabetes mellitus, hypertension, having ever smoked tobacco, history of cerebrovascular accident or myocardial infarction. The Short Form 36 Scale of Physical Function (SF36-PF), a continuous 0–100 scale, was used to assess physical function(10). Time-varying predictors were assessed at each interview.

Study sample

To focus on depression risk among young adults, our sample included all LOS participants under age of 45 at the time of interview (N=618). Seventy-two subjects (12%) were dropped for missing responses to key disease activity variables. These subjects were more likely to have had a myocardial infarction (15% v. 7%, p=0.01), more likely to be receiving dialysis (18% v. 9%, p=0.02), and less likely to have major depression (28% v. 47%, p=0.002) than retained subjects, but they did not differ in the proportion of childhood-onset disease. The final sample size was 546. As depression is subject to year-to-year variation, each participant could contribute observations from up to 12 interviews. Participants were censored after age 45. The final analysis included 2923 observations, or an average of 5.3 observations per participant. 64% of participants completed the final study interview, with no difference in dropout rates between cSLE and aSLE participants.

Statistical analysis

Baseline characteristics of the cSLE and aSLE groups were summarized and compared with bivariate statistics (Student’s t-test, rank sum and chi-square test), as appropriate. In order to account for multiple observations per participant, we used general estimating equations to fit a logistic regression model of the likelihood of major depression across all 12 waves of the LOS. We calculated adjusted and unadjusted odds ratios and the period prevalence, which was based on predicted marginals from the regression models. Childhood-onset SLE, gender, and race/ethnicity were included as fixed covariates. Time-varying predictors included age, marital status, educational attainment, poverty, disease duration, disease activity, current steroid use, current dialysis, physical function, diabetes mellitus, hypertension, any history of myocardial infarction or stroke, and any history of smoking. We

included in the final models age, gender, race/ethnicity, and all predictors of major depression with p<0.2 in bivariate analysis. Disease duration was categorized in multivariate analyses (0–10 years, 11–20 years, and >20 years) to account for the collinear relationship among age of onset, current age and disease duration. Individuals' total number of interviews contributed was included as a covariate to account for variation among participants. We also tested for an interaction and estimated the combined marginal effect (period prevalence) of childhood-onset SLE and educational attainment on the probability of depression, as previous studies of the LOS have shown depression to correlate with educational status. Finally, to evaluate the likelihood of recurrent major depression, we analyzed data for participants who had completed two or more annual CES-D assessments, to calculate unadjusted and adjusted odds ratios and prevalence for major depression at two or more assessments. All analyses were performed using STATA 13.0 (StataCorp, College Station, TX.)

RESULTS

Subject characteristics

Among 546 participants with SLE between the ages of 18 and 45, 115 (21%) had cSLE (Table 1). Participants with cSLE were on average younger, with more males (13% versus 5%, p=0.003) and fewer white individuals (39% versus 52%, p=0.02). Differences in clinical characteristics between aSLE and cSLE groups at baseline were consistent with previous analyses of the LOS. Subjects with cSLE had a longer mean disease duration (13±7 versus 8±6 years,) ranging from 0 to 25 years in the aSLE group and 1 to 28 years in the cSLE group. A greater proportion of subjects with cSLE required dialysis (17% versus 7%, p=0.002) or had undergone renal transplant (11% versus 3%, p<0.001). However, disease activity was lower among cSLE participants (mean SLAQ score 9 versus 12, p<0.001), and physical function was better (mean SF36-PF score 51 versus 44, p<0.001).

Prevalence of depression

47% of participants met criteria for major depression at least once during the study period. In bivariate analysis, there was no difference between cSLE and aSLE groups in baseline prevalence of major depression, or in the likelihood of major depression at any point in the study. In multivariate repeated measures analysis, participants with cSLE were more likely to exhibit major depression compared to those with aSLE (OR 1.7, 95% CI 1.0–2.7, Table 2).

Predictors of depression

Lower educational attainment, higher disease activity, lower physical function, and history of smoking were all significant predictors of depression in both unadjusted and adjusted analyses. Older age predicted depression in adjusted analysis only. Several covariates predicted depression in unadjusted analysis only: higher BMI, diabetes mellitus, hypertension, history of myocardial infarction or stroke, currently steroid use, current dialysis dependence or living in poverty. Disease duration did not predict major depression in this population. There was a significant interaction between childhood-onset SLE and

educational attainment in the adjusted prevalence of major depression (Figure 1); individuals with cSLE had a higher prevalence of major depression in all educational groups.

Predictors of recurrent depression

To evaluate the likelihood of recurrent depression, we analyzed data for participants with two or more assessments of depression (N=526). Twenty participants (2 cSLE and 18 aSLE) with only one completed assessment for depression were dropped from this analysis. There was no significant difference in the likelihood of cSLE vs. aSLE among excluded participants. In bivariate analysis, the prevalence of recurrent major depression was 32% for individuals with cSLE, compared to 29% of individuals with aSLE. Participants with cSLE were significantly more likely exhibit recurrent major depression in adjusted analyses (OR 2.2, 95% CI 1.2–4.3). The adjusted prevalence of major depression at multiple measurements was 39% among participants with cSLE and 29% among those with aSLE ($p<0.001$). Educational attainment and disease activity were associated with increased odds of major depression at multiple assessments in both unadjusted and adjusted analyses; age, steroid use, poorer physical function, higher BMI, diabetes mellitus, hypertension and history of smoking were significant predictors in unadjusted analyses only.

DISCUSSION

We present results from a large, prospective longitudinal cohort study of young adults with SLE, examining the risk of major depression and associated risk factors. Comorbid depression may exacerbate the challenges that young adults with SLE face with managing chronic illness, and pediatric onset of SLE may exert a lasting additive effect on long-term depression risk. Our findings provide new insight into the relationship of major depression to pediatric-onset disease and educational attainment in young adults with SLE, emphasizing the need for early mental health intervention in this population to optimize outcomes.

We found that almost half of young adults with SLE were affected by major depression over the 12 years of the current study, and that the adjusted risk was greater for those with cSLE as compared to aSLE. Consistent with previous LOS analyses indicating disease activity as the SLE-specific characteristic most associated with incident depression(3), we found that disease activity was associated with major depression. However, cSLE was an independent risk factor for major depression even after adjusting for disease activity and duration. These results suggest that the increased depression risk associated with childhood-onset disease is not entirely due to greater SLE activity or damage. Given the typical onset of cSLE in adolescence, a critical time for neurocognitive development, along with childhood stress experienced due to chronic disease and its treatment, it is possible that cSLE may adversely impact psychological development. Future examination of the developmental impact of cSLE may yield insight into the mechanism of differential depression risk among cSLE and aSLE patients.

Interestingly, lower educational attainment was the demographic predictor most strongly associated with major depression in our young adult SLE cohort. This effect occurred in a dose-dependent fashion, independent of poverty status, and was greater for those with cSLE compared to aSLE. National US data indicates that students with internalizing disorders

such as depression have a lower odds of graduating high school and of going to college(11). Alternatively, lower educational attainment may lead to subsequent onset of depression, as increased education has been associated with better social functioning and coping skills(12).

Overall, our findings suggest that young adults with SLE are at high risk for major depression. Early detection and treatment is likely to promote remission of depression, and to improve both clinical and psychosocial outcomes(13). Rheumatologists, often acting as primary providers for patients with SLE, may have an important role in depression screening, which is recommended for all adolescents and adults by the United States Preventive Services Task Force (www.uspreventiveservicestaskforce.org). Resources for depression screening include the free 9-item Patient Health Questionnaire (PHQ-9), which is available in Spanish, and as a modified version for adolescents. The American Academy of Pediatrics also offers web-based resources for behavioral health screening. Access to behavioral health providers may be improved through advocating for rheumatology-based social workers and psychologists, and strengthening communication with community-based psychosocial resources.

Additionally, enhanced educational supports for youth with SLE may promote grade-level achievement and continuation of education, with protective benefits against depression and associated adverse health outcomes. Mentoring programs and strategies to enhance patients' school connectedness, such as disease education for school staff and peers, have shown protective effects for college graduation in youth with chronic illness(14). As cSLE patients have demonstrated greater risk for unemployment(15), concurrent depression intervention and educational supports may also improve vocational outcomes.

The strengths of our study include the large SLE cohort and longitudinal collection of detailed health data over 12 years; however, it is not without limitations. First, as the LOS is not an inception cohort, there may be selection bias for healthier subjects choosing to participate in the study, as well as a survival effect in which surviving cSLE subjects available to participate in the study may represent a healthier cohort. However, we would expect these effects to bias our findings towards the null. Second, the generalizability of our findings may be limited, as the LOS is less representative of African-Americans than other US SLE samples. Third, reporting bias is possible due to inaccuracies in the self-reported LOS data. Although the LOS self-reported outcomes have been validated through chart review, we were not able to evaluate the effect of depression treatment due to poor reliability of these data in the LOS. Last, we were not able to establish causality of associations between major depression and risk factors, as these analyses did not assess the timing of onset of depression relative to risk factors.

CONCLUSION

Young adults with SLE are at high risk for major depression, which is strongly associated with lower educational attainment. The impact is greater in young adults with childhood-onset vs adult-onset SLE. Early depression screening and treatment targeted to young adults with SLE may improve both medical and psychosocial outcomes in this vulnerable population.

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SIGNIFICANCE AND INNOVATIONS

- Young adults with SLE, particularly those with childhood-onset disease, are at high risk for major depression.
- Patients with high levels of disease activity, poor physical function, low educational attainment may be at significantly increased risk for depression.
- Early depression screening and treatment targeted to young adults with SLE, especially those with cSLE, have the potential to improve both medical and psychosocial outcomes in this vulnerable population.

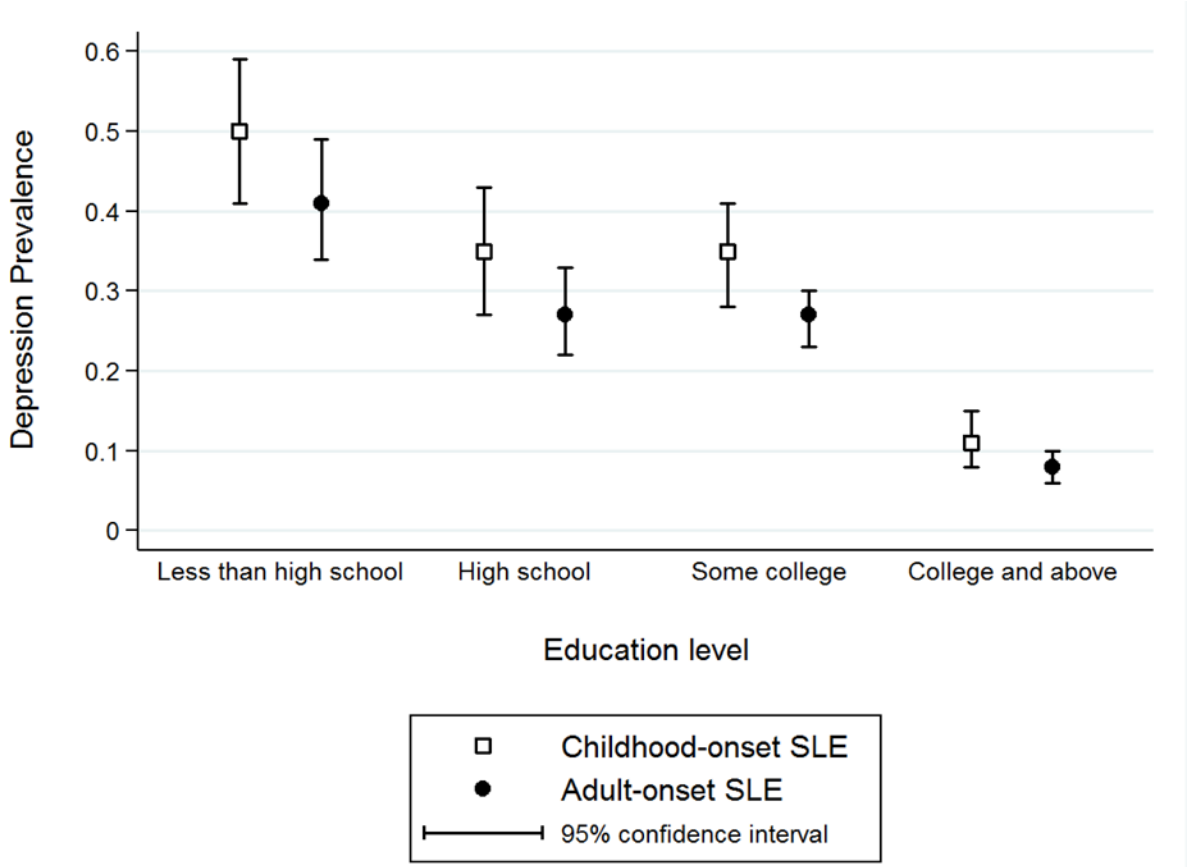

Figure 1. 12-year period prevalence of major depression stratified by educational attainment among participants with cSLE and aSLE in the LOS*

* Depression defined as high levels of self-reported depressive symptoms (CESD≥24) suggestive of major depression. Period prevalence of depression over the 12 years of study observation was calculated based on predicted marginals from the regression models.

Table 1

Subject characteristics at baseline by age at SLE diagnosis in the Lupus Outcomes Study.

Variable	cSLE (N=115)	aSLE (N=431)	*P*
	N (%) or Mean (± SD)		
Sociodemographics			
Age (years)	27 (±7)	36 (±6)	<0.001
Female	100 (87)	409 (95)	0.003
Race/Ethnicity			0.09
White	45 (39)	222 (51)	
Latino	23 (20)	62 (14)	
African American	11 (10)	51 (12)	
Asian	23 (20)	62 (14)	
Other	13 (11)	34 (8)	
Married	39 (34)	245 (57)	<0.001
Education			0.01
Bachelor's or postgraduate degree	35 (30)	173 (40)	
Some college or vocational degree	46 (40)	187 (43)	
High school diploma or equivalent	26 (22)	50 (12)	
Did not complete high school	8 (7)	21 (5)	
Employed	55 (48)	249 (58)	0.06
Living in poverty *	17 (15)	70 (16)	NS
SLE Characteristics			
Age at diagnosis (years)	14 (± 3)	27 (± 6)	<0.001
Disease duration (years)	13 (± 7)	8 (± 6)	<0.001
Disease activity (SLAQ) **	9 (± 8)	12 (± 8)	<0.001
Steroid use currently	114 (99)	392 (90)	0.003
Dialysis currently	19 (17)	31 (7)	0.002
History of renal transplant	13 (11)	14 (3)	<0.001
General Health Characteristics			
Physical function (SF36-PF) *** *median (range)*	51 (17–57)	44 (15–57)	<0.001
BMI	25 (± 5)	26 (± 7)	NS
Diabetes Mellitus	9 (8)	23 (5)	NS
Hypertension	49 (42)	162 (38)	NS
History of smoking	26 (23)	138 (32)	0.05
History of MI or stroke	12 (10)	26 (6)	0.1

* Income below 125% of the Federal poverty level;

** SLAQ = Systemic Lupus Activity Questionnaire (0-47, higher score indicates more disease activity);

*** SF36-PF = SF-36 Scale of Physical Functioning (0–100, higher score indicates better physical functioning).

Table 2

Unadjusted and adjusted odds ratios for the presence of major depression among individuals age 18–45 with SLE (N=546)[†]

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[†]
Childhood-onset SLE	0.8 (0.5–1.1)	**1.7 (1.0–2.7)**
Sociodemographics		
Age (years)	1.01 (0.99–1.02)	**1.04 (1.01–1.07)**
Female	1.5 (0.8–2.9)	0.9 (0.5–1.6)
Non-white ethnicity	1.2 (0.9–1.6)	1.2 (0.8–1.7)
Unmarried	1.1 (0.9–1.3)	1.1 (0.9–1.5)
Education		
Bachelor's or postgraduate degree	*reference*	*reference*
Some college or vocational degree	**3.2 (2.5–4.1)**	**2.0 (1.4–2.8)**
High school diploma or equivalent	**3.5 (2.5–4.8)**	**2.1 (1.4–3.3)**
Did not complete high school	**5.4 (3.4–8.6)**	**2.5 (1.5–4.2)**
Living in poverty[*]	**1.7 (1.3–2.2)**	1.0 (0.7–1.4)
SLE Characteristics		
Disease duration, categorized[^]		
20+ years	*reference*	*reference*
11–20 years	1.1 (0.9–1.7)	1.0 (0.7–1.4)
0–10 years	1.2 (0.8–1.5)	1.0 (0.6–1.7)
Higher disease activity (SLAQ)[**]	**1.14 (1.12–1.16)**	**1.11 (1.09–1.14)**
Steroid use currently	**1.4 (1.2–1.7)**	1.1 (0.8–1.4)
Dialysis currently	**1.6 (1.2–2.1)**	1.2 (0.8–1.9)
History of renal transplant[#]	1.1 (0.6–1.9)	–
General Health Characteristics		
Lower physical function (SF36-PF)[***]	**1.06 (1.05–1.07)**	**1.03 (1.01–1.04)**
Higher BMI	**1.04 (1.02–1.05)**	1.00 (0.98–1.02)
Diabetes mellitus	**2.0 (1.2–3.3)**	1.3 (0.7–2.2)
Hypertension	**1.5 (1.2–1.8)**	1.1 (0.8–1.5)
History of smoking	**1.6 (1.3–2.1)**	**1.3 (1.0–1.8)**
History of myocardial infarction or stroke	**2.2 (1.4–3.2)**	1.6 (0.7–3.3)

[†] Shown are odds ratios (OR) with 95% confidence intervals (CI) adjusted for variables shown plus number of interviews contributed.

[*] Income below 125% of the Federal poverty level;

[**] SLAQ = Systemic Lupus Activity Questionnaire (0–47, higher score indicates more disease activity);

[***] SF36-PF = SF-36 Scale of Physical Functioning (0–100)

[^] Disease duration categorized for inclusion in the multivariate model to account for the collinear relationship among age of onset, current age and disease duration.

[#] History of renal transplant not included in the final multivariate model because p>0.2 in bivariate analysis.