Identifying Differences in Risk Factors for Depression and Anxiety in Pediatric Chronic Disease: A Matched Cross-Sectional Study of Youth with Lupus/Mixed Connective Tissue Disease and Their Peers with Diabetes

Andrea Knight, MD, MSCE[1,2,3], Pamela Weiss, MD, MSCE[1,2,4], Knashawn Morales, ScD[4], Marsha Gerdes, PhD[3,5], Melissa Rearson, MSN, CRNP[6], Michelle Vickery, MPH[2,3], and Ron Keren, MD, MPH[2,4,5]

Objective To investigate differences in risk factors for depression and anxiety, such as central nervous system involvement in systemic lupus erythematosus (SLE)/mixed connective tissue disease (MCTD), by comparing youth with SLE/MCTD to peers with type 1 diabetes mellitus (T1D).

Study design We conducted a cross-sectional study of 50 outpatient pairs, ages 8 years and above, matching subjects with SLE/MCTD and T1D by sex and age group. We screened for depression, suicidal ideation, and anxiety using the Patient Health Questionnaire-9 and the Screen for Childhood Anxiety Related Emotional Disorders, respectively. We collected parent-reported mental health treatment data. We compared prevalence and treatment rates between subjects with SLE/MCTD and T1D, and identified disease-specific risk factors using logistic regression.

Results Depression symptoms were present in 23%, suicidal ideation in 15%, and anxiety in 27% of participants. Compared with subjects with T1D, subjects with SLE/MCTD had lower adjusted rates of depression and suicidal ideation, yet poorer rates of mental health treatment (24% vs 53%). Non-White race/ethnicity and longer disease duration were independent risk factors for depression and suicidal ideation. Depression was associated with poor disease control in both groups, and anxiety with insulin pump use in subjects with T1D.

Conclusion Depression and anxiety are high and undertreated in youth with SLE/MCTD and T1D. Focusing on risk factors such as race/ethnicity and disease duration may improve their mental health care. Further study of central nervous system and other disease-related factors may identify targets for intervention. *(J Pediatr 2015;167:1397-403)*.

See editorial, p 1192

Chronic disease presents both physical and emotional challenges for affected children and adolescents. Pediatric-onset systemic lupus erythematosus (SLE) and the SLE-like syndrome of mixed connective tissue disease (MCTD) are chronic autoimmune diseases associated with high morbidity and mortality due to the multi-organ damage, particularly due to central nervous system (CNS) and renal involvement, as well as high-risk immunosuppressive treatment.[1] In contrast to the prevalence of depression in 11%, suicidal ideation in 6%, and anxiety in 8% of the US general adolescent population,[2,3] these disorders occur in up to 60%, 20%, and 35%, respectively, of youth with SLE/MCTD.[4-6] Even though the cause of this remains unclear, potential reasons include social, cultural, and genetic factors in the predominantly non-White population with SLE/MCTD, the psychological burden of chronic disease, effects of steroid treatment, and CNS inflammation, which is recognized as a cause of mood and anxiety disorders in SLE.[7] Among youth with SLE/MCTD and other chronic disease, there is little known about differences in depression and anxiety etiology between disease groups, and elucidating the contributing factors may guide more effective recognition and treatment of these conditions in these patients. This is of critical importance, as depression and anxiety in chronic disease have been shown to negatively impact clinical and psycho-

CHOP	Children's Hospital of Philadelphia
CNS	Central nervous system
HbA1c	Hemoglobin A1c
MCTD	Mixed connective tissue disease
PHQ-9	Patient Health Questionnaire-9
QOL	Quality of life
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus Disease Activity Index
T1D	Type 1 diabetes mellitus

From the [1]Division of Rheumatology, [2]Center for Pediatric Clinical Effectiveness, [3]Children's Hospital of Philadelphia PolicyLab, Children's Hospital of Philadelphia; [4]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania; and Divisions of [5]General Pediatrics and [6]Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA

Funded by the National Institutes of Health (5T32HD060550-03 [to A.K.]), US Health Resources and Services Administration (D34HP24459), Center of Excellence for Diversity in Health Education and Research, Perelman School of Medicine, US Health Resources and Services Administration (institutional grant D34HP24459 [to A.K.]), and Lupus Foundation of America Tri-State Chapter Anna Louise Harmon Preceptorship (to A.K.). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.07.048

social outcomes, resulting in poorer disease control, quality of life (QOL), school performance, transition to adult care, work productivity, and greater healthcare utilization and costs.[8-12]

To explore the role of disease-specific factors in depression and anxiety in youth with SLE/MCTD, we compared these patients with youth with type 1 diabetes mellitus (T1D), who are similar in their burden of life-threatening disease, potential multi-organ involvement, and requirement for lifelong systemic medication, but different in their lower risk for direct CNS inflammation. In the setting of emerging knowledge of the role of inflammation in psychiatric disorders,[13,14] we sought to investigate differences in depression and anxiety between these chronic disease groups with known differential risk for CNS inflammation. Using a matched analysis to eliminate confounding by sex and age, which have known associations with both SLE/MCTD[1] and depression/anxiety,[2] we specifically aimed to compare youth with SLE/MCTD and T1D with respect to: (1) prevalence of depression, suicidal ideation, and anxiety symptoms; (2) rate of mental health treatment in those with symptoms; and (3) association of depression and anxiety symptoms with disease-specific factors. We hypothesized that: (1) subjects with SLE/MCTD would have a higher prevalence of depression and anxiety than subjects with T1D; (2) rates of mental health treatment would not differ; and (3) depression and anxiety would be associated with higher disease burden in both cohorts.

Methods

We conducted a cross-sectional analysis of outpatient youth with SLE/MCTD and T1D at the Children's Hospital of Philadelphia (CHOP). The two cohorts were matched by sex and age group to eliminate confounding by these factors because pediatric-onset SLE is known to be more prevalent in adolescent females[1] and the incidence of childhood depression and anxiety peaks in adolescent females.[2] Age was grouped according to the American Academy of Pediatrics developmental stages[15] as follows: age pre-adolescent (8-11 years inclusive), adolescent (12-17 years inclusive), young adult (18 years and above). Subjects with SLE/MCTD were consecutively recruited during routine rheumatology and nephrology outpatient visits between June 2012 and May 2013. Subjects had a diagnosis of pediatric-onset SLE if ≥4 of 11 SLE classification criteria[16] were fulfilled prior to the 18th birthday. Subjects had a diagnosis of pediatric-onset MCTD if they met either Kahn or Alarcon–Segovia criteria[17] prior to the 18th birthday. Exclusion criteria were: age <8 years; limited English proficiency, cognitive or communication deficit precluding questionnaire completion; isolated cutaneous lupus. Of 67 eligible subjects approached, 50 (75%) consented to the study. Subjects with T1D had a diagnosis of T1D documented in the medical chart and were consecutively recruited from March 2014 to September 2014 during routine outpatient visits to the CHOP Diabetes Center for Children. Exclusion criteria were: age <8 years; limited English proficiency; cognitive or communication deficit precluding questionnaire completion; current steroid use; SLE or MCTD diagnosis. Of 66 eligible subjects approached, 50 (76%) consented to the study. Informed consent from all participants and approval from the CHOP Institutional Review Board was obtained before initiating the study.

We used cohort group (SLE/MCTD vs T1D) as the measure of exposure for comparisons of mental health symptom prevalence and treatment rates. For both cohorts, we calculated depression, suicidal ideation, and anxiety prevalence as the primary outcome. We screened for depression symptoms using the Patient Health Questionnaire-9 (PHQ-9), a 9-item self-administered depression screening module based on the *Diagnostic and Statistical Manual IV* criteria for major depression previously validated in the general adolescent population.[18] Each item assesses feelings over the previous 2 weeks, and is scored from 0 (not at all) up to 3 (nearly every day). Scores range from 0 to 27. A positive depression screen was defined as a score ≥5 on the PHQ-9 and included scores in the mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27) ranges.[19] A score of ≥1 on item 9 of the PHQ-9 questionnaire was considered indicative of suicidal ideation and also considered a positive depression screen regardless of total PHQ-9 score; however, these positive screens were not categorized for depression severity if the total PHQ-9 was <5. We screened for anxiety symptoms using the Screen for Childhood Anxiety Related Emotional Disorders, a self-administered 41-item anxiety screening tool, previously validated in outpatient children and adolescents.[20] Each item assesses feelings over the previous 3 months with 3 possible responses: "not true or hardly ever true" (score of 0), "somewhat true or sometimes true" (score of 1), and "very true or often true" (score of 2). Scores totaling ≥25 indicate a positive screen for anxiety symptoms. Summed scores for item subgroups also indicate the following specific features: generalized anxiety, panic/somatic symptoms, separation anxiety, social anxiety, and school avoidance. Depression and anxiety screening was performed using REDCap electronic survey and data capture tools hosted at CHOP.[21] Upon identification of depression or anxiety symptoms, an educational handout was provided to the family with mental health care referral information. Identified suicide risk was addressed with a suicide prevention protocol consisting of immediate direct questioning of suicidal intent, and plan or attempt within the prior week; endorsement of any of these prompted development of a safety plan and urgent referral for immediate psychology/psychiatry evaluation. We included self-reported mental health treatment (Yes/No) in those with any symptom (depression, suicidal ideation, or anxiety) as a secondary outcome. Assessed by parent/legal guardian survey, treatment included a history of a previous psychiatric diagnosis, use of psychiatric medications, or previous care by a psychiatrist or psychologist in the preceding 12 months.

The following variables were collected by survey of the parents/legal guardians for all subjects: race/ethnicity, highest