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A systematic review and meta-analysis of cutaneous manifestations in late- versus early-onset systemic lupus erythematosus

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ABSTRACT

Objectives: Although systemic lupus erythematosus (SLE) most commonly occurs in reproductive-age women, some are diagnosed after the age of 50. Recognizing that greater than one-third of SLE criteria are cutaneous, we undertook a systematic review and meta-analysis to evaluate differences in cutaneous manifestations in early- and late-onset SLE patients.

Methods: We searched the literature using PubMed, CINAHL, Web of Science, and Cochrane Library. We excluded studies that did not include ACR SLE classification criteria, early-onset controls, that defined late-onset SLE as <50 years of age, or were not written in English. Two authors rated study quality using the Newcastle Ottawa Quality Scale. We used Forest plots to compare odds ratios (95% CI) of cutaneous manifestations by age. Study heterogeneity was assessed using I^2.

Results: Overall, 35 studies, representing 11,189 early-onset and 1727 late-onset patients with SLE, met eligibility criteria. The female:male ratio was lower in the late-onset group (5:1 versus 8:1). Most cutaneous manifestations were less prevalent in the late-onset group. In particular, malar rash [OR = 0.43 (0.35, 0.52)], photosensitivity [OR = 0.72 (0.59, 0.88)], and livedo reticularis [OR = 0.33 (0.17, 0.64)] were less common in late-onset patients. In contrast, sicca symptoms were more common [OR = 2.45 (1.91, 3.14)]. The mean Newcastle Ottawa Quality Scale score was 6.3 $\pm$ 0.5 (scale: 0–9) with high inter-rater reliability for the score (0.96).

Conclusions: Overall, cutaneous manifestations are less common in late-onset SLE patients, except sicca symptoms. Future studies should investigate etiologies for this phenomenon including roles of immune senescence, environment, gender, and immunogenetics.

Introduction

Systemic lupus erythematosus (SLE) most often occurs in women of reproductive-age. SLE onset in adults ≥ 50 years old is referred to as "late-onset SLE." Previous studies report that late-onset SLE patients are more likely to include men and have a more insidious onset of disease [1–7]. Over one-third of the ACR SLE classification criteria reflect cutaneous manifestations, so it is not surprising that arthritis and cutaneous findings remain the most common presenting symptoms in both late-onset and early-onset SLE. Yet, previous literature suggested that these are less common in late-onset disease [3,8–12]. Overall, the proportion of late-onset SLE among all SLE cases is relatively low, ranging from 4% to 20% [1,3,4,8,10,13,14]. However, due to a higher life expectancy and increasing awareness of the disease, the prevalence of late-onset SLE is expected to rise. Therefore, identifying the unique characteristics of this patient population is important. Conclusions drawn from previous studies including a 1989 meta-analysis of nine studies with 170 late-onset SLE patients [15] were limited by small sizes and heterogeneity of patient groups. To gain additional insight into the cutaneous manifestations of late-onset SLE, we conducted a systematic review and meta-analysis of published literature. We compared cutaneous manifestations in patients with early and late-onset SLE.

Methods

We performed a systematic review of the literature to identify articles comparing the cutaneous manifestations of patients with

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late versus early-onset lupus. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consensus was followed in the completion of this systematic review and meta-analysis [16]. With assistance from a professional medical librarian we electronically searched the literature in PubMed, CINAHL, Web of Science and Cochrane Library with MESH, and keyword subject headings "systemic lupus erythematosus," "cutaneous lupus erythematosus," "SLE," or "late-onset SLE," and "age factors," "age of onset," "late-onset," "older-onset," "over 50," "older adults," and "geriatrics," for entries published from databases' inception through August 2013. Potential articles were reviewed first by title and abstract only, next by full text, and lastly by analyzing eligible studies in detail. A second reviewer scrutinized a random 10% of all potential titles and abstracts. The reviewers demonstrated 100% agreement in articles included and excluded. Bibliographies of all included articles were reviewed to identify additional citations.

Studies with the following criteria were included: (A) confirmed SLE using American College of Rheumatology (ACR) criteria [17] and (B) data on cutaneous findings of late-onset SLE defined as ≥ 50 years of age. We excluded studies that did not require SLE patients to meet ACR classification criteria, did not include early-onset controls, defined late-onset SLE as <50 years of age, or were written in a language other than English (Fig. 1).

Methodological quality of eligible studies and risk of bias were evaluated using the Newcastle Ottawa Quality Assessment Scale for cohort and case–control studies [18]. The scale assesses cohort selection and comparisons between groups (cases and controls), outcomes, and adequacy of follow-up. Two reviewers rated each study, assigning a score out of nine possible points. Discrepancies in scores were resolved by consensus with a third MD reviewer. Inter-rater reliability of two reviewers was calculated.

Data was extracted by two authors including date of publication, study location (country and population versus hospital or clinic based), study type (cohort versus case study), follow-up period, late-onset age definition, and clinical manifestations. The numbers of late-onset patients who exhibited SLE cutaneous manifestations including malar rash, discoid rash, photosensitivity, mucosal ulceration, alopecia, sicca symptoms, Raynaud's phenomenon, cutaneous vasculitis, livedo reticularis, and subacute cutaneous lupus (SCLE) were recorded and compared to numbers of these manifestations in early-onset patients.

Statistical analysis

We created Forest plots to summarize composite data, generating odds ratios and corresponding 95% CI for each cutaneous manifestation. Heterogeneity between studies was evaluated using the I^2 statistic with 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Funnel plots were reviewed to detect publication bias. We performed additional sub-group analyses for Forest plots demonstrating $>30\%$ heterogeneity, excluding case–control studies and determining the relative risk of the cutaneous manifestation. All analyses were performed using R software version 3.1.2 and the package "meta."

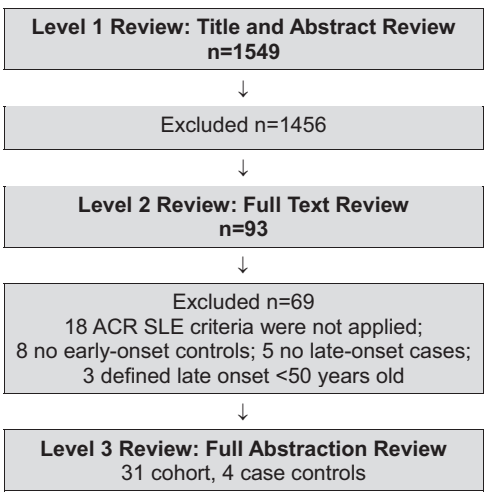

Fig. 1. Study selection process with description of study inclusion and exclusions during the three level review for the systematic review and meta-analysis.

Results

Literature searches yielded 1549 potential articles. After screening titles and abstracts, 95 full articles were retrieved for full-text evaluation. After application of exclusion criteria, 35 articles met criteria for final inclusion and level 3 review (Fig. 1), including 31 cohort studies and four case–control studies [1–14,19–39].

The 35 studies included in the systematic review and meta-analysis are summarized in Table 1. Studies reflected a geographically and ethnically diverse population. Overall, 27 studies used the classic inclusion of age ≥ 50 years, while the remaining eight had definitions ranging from >50 to >65 years. Of note, 24 of the 35 studies also included individuals <18 years of age in the control group. The mean $\pm$ standard deviation Newcastle Ottawa Quality Scale score of the 35 included articles was 6.3 ± 0.45 with a maximum possible score of 9 points. Inter-rater reliability for these quality scores was $k = 0.96$ with two independent MD reviewers.

Our pooled cohorts included 1727 patients with late-onset SLE and 11,189 early-onset controls. Female pre-dominance was greater in the early-onset group compared to the late-onset group (89% versus 83%, $p < 0.001$).

Meta-analysis results

Random effects models were performed for each cutaneous manifestations to compare prevalence in late versus early-onset SLE (Table 2). First, we examined results of Forest plots for the manifestations included as ACR classification criteria as shown in Figure 2. In the random effects model, malar rash was significantly less common in late-onset, compared to early-onset, SLE patients [OR = 0.43 (0.35, 0.52)]. Due to study heterogeneity ($I^2 = 64\%$, $p < 0.0001$), we performed sensitivity analysis by omitting the case–control studies. The subsequent relative risk of malar rash was similar [RR = 0.65 (0.57, 0.73)]. Photosensitivity was also significantly less common in late-onset SLE patients [Fig. 2, OR = 0.72 (0.59, 0.88)]. Again, due to observed heterogeneity ($I^2 = 53.5\%$, $p < 0.0002$), sensitivity analysis was performed and when excluding case–control studies, the relative risk of photosensitivity was nearly identical to the OR derived from inclusion of all studies [RR = 0.85 (0.75, 0.96)]. Odds of mucosal ulceration was similar in young and late-onset SLE [OR = 0.88 (0.74, 1.04)] with low heterogeneity between studies ($I^2 = 22.2\%$, $p = 0.14$). The composite OR for discoid rash was similar in early and late-onset SLE patients (OR = 1.11 [0.91, 1.34]) with low-study heterogeneity ($I^2 = 9.2\%$, $p = 0.33$).

We next compared the age-related prevalence of cutaneous manifestations that are not part of the ACR diagnostic criteria for SLE. The composite OR for sicca symptoms was significantly higher in late-onset SLE patients [OR = 2.45 (1.91, 3.14)] with low heterogeneity ($I^2 = 13.1\%$, $p = 0.31$) (Fig. 3). Raynaud's phenomenon and alopecia were significantly less likely in late-onset SLE patients [OR = 0.84 (0.71, 0.99) and OR = 0.63 (0.48, 0.82)], respectively (Fig. 3) both with low heterogeneity. The odds ratios for cutaneous vasculitis, livedo reticularis, and SCLE were similar in early and late-onset patients (Fig. 3).