Differences in Autoantibody Profiles and Disease Activity and Damage Scores Between Childhood- and Adult-Onset Systemic Lupus Erythematosus: A Meta-Analysis

Brieanna Livingston, BSc Hon,*,[1] Ashley Bonner, BSc Math,†,[2] and Janet Pope, MD, MPH, FRCPC*,‡

Background: Age at systemic lupus erythematosus (SLE) onset may impact autoantibodies, disease activity, and damage. A meta-analysis of all studies that directly compared childhood-onset lupus (cSLE) to adult-onset lupus was performed to determine which autoantibodies and whether activity and damage scores vary between adult- and pediatric-onset SLE.

Methods: A literature search of the MEDLINE/PubMed, EMBASE, CINAHL, and SCOPUS databases (until January 2011) was conducted to identify relevant articles. Study quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology checklist. Two independent reviewers determined eligibility criteria. Pooled odds ratios and mean differences were calculated assuming random effects, and heterogeneity was estimated and presented as (odds ratios; 95% confidence interval).

Results: Of the 484 studies identified, 19 were eligible. The total number of patients was 7519. Mean trial quality was 18/32, ranging from 8 to 29. Several statistically significant differences were found: more frequently positive anti–dsDNA antibody (1.97; 1.31 to 2.96) and IgG/IgM anticardiolipin antibody (1.66; 1.20 to 2.28), and mean disease activity scores (SLE Disease Activity Index) (4.73; 2.13 to 7.32) were higher in cSLE. Disease damage [SLE damage index (SDI)] was lower in cSLE, but not significantly (0.50; −0.13 to 1.14). Rheumatoid factor was increased in adults (0.53; 0.32 to 0.87). The frequency of the autoantibodies and laboratories was not different between the groups (ANA, anti-Smith, anti-RNP, anti-U1RNP, anti-Ro and anti-La, antiphospholipid, lupus anticoagulant, complements, ssDNA, and Coomb's test).

Conclusions: The results of this meta-analysis suggest that cSLE may have different autoantibody profiles (increased anti–dsDNA and anticardiolipin antibody, less rheumatoid factor), and more disease activity than adult-onset SLE. Damage may be less in children, but larger studies are needed.

 Semin Arthritis Rheum 42:271-280

Keywords: *SLE (lupus, systemic lupus erythematosus), adult, pediatric, differences, autoantibodies, SLE disease activity, SLEDAI, SLE damage index (SLICC SDI)*

Systemic lupus erythematosus (SLE) is a disease that impacts multiple body systems. Clinical manifestations range from skin and joint involvement to life-threatening kidney and neurologic disease. SLE is characterized by the presence of autoantibodies. Autoantibodies are used for diagnosis, correlate with clinical manifestations, and provide important prognostic information (1).

Usually, SLE begins in women during the second to fourth decades of life; however, 15% to 20% of SLE begins in childhood (2). A recent meta-analysis compared clinical manifestations between child-onset SLE (cSLE) and adult-onset SLE (aSLE): fever, malar rash, some he-

*Western University of Canada, Schulich School of Medicine and Dentistry, London, Ontario, Canada.
†McMaster University, Hamilton, Ontario, Canada.
‡Division of Rheumatology, Department of Medicine, St. Joseph's Health Care, London, Ontario, Canada.

[1]Canadian Rheumatology Association (CRA) Roche Research Summer Studentship Award.
[2]Amgen Summer Studentship Award.

Address reprint requests to Janet Pope, MD, MPH, FRCPC, Professor of Medicine, Division Head, Rheumatology, University of Western Ontario, Schulich School of Medicine and Dentistry, 268 Grosvenor Street, London, Ontario, N6A 4V2, Canada. E-mail: janet.pope@sjhc.london.on.ca.

0049-0172/12/$-see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.semarthrit.2012.05.001

matologic measures (hemolytic anemia and thrombocytopenia), lymphadenopathy, and renal disease were more common in cSLE, whereas Raynaud's, pleuritis, and sicca syndrome were more common in aSLE (3). Age at disease onset may also impact the autoantibodies, disease activity, and disease damage in SLE (4). Two commonly used indexes, SLE disease activity index (SLEDAI) and SLE damage index (SDI), measure disease activity and disease damage, respectively (5-7). These scales have been validated for use in both adults and children (8-10); however, there is also a modified SDI in cSLE, which adds growth failure (M-SDI) (11).

The objectives of this study were to conduct a systemic literature review and meta-analysis of all studies that directly compared cSLE to aSLE to determine (1) which autoantibodies and laboratory tests varied with age at disease onset, and (2) if activity and damage was different as measured by SLEDAI and SDI scores.

MATERIALS AND METHODS

Identification of Studies

A similar search strategy and methods have been described in a companion meta-analysis of clinical manifestations between cSLE and aSLE (3). A comprehensive literature search of the MEDLINE/PubMed, EMBASE, CINAHL, and SCOPUS databases was conducted (each from database inception to January 2011) using the following search terms: Systemic lupus erythematosus and Age factors/or Onset age/or Age of onset/or Age differences and Adult and Child. In addition, key references were hand searched to identify potentially relevant studies. Studies were included if they (1) compared autoantibody profiles, laboratory tests, SLEDAI scores, or SDI scores of cSLE to aSLE, (2) provided numerical data (numbers or percentages) of the incidence or prevalence of these variables, (3) were published in English, and (4) were not published before 1982. Studies published before 1982 were not included because, prior to this, the revised American College of Rheumatology criteria for the classification of SLE had not been published (12). Studies were excluded if they (1) contained comparative data, but not on a variable of interest (eg, mortality, ethnicity), or (2) examined a subset of patients (eg, only patients with kidney involvement). If more than 1 identified study used the same study population, the most recent of the studies was included. If publications from the same group reported different manifestations, each publication was used for nonredundant items. Two reviewers separately included articles using the inclusion and exclusion criteria (BL and JP). If there was disagreement, the full articles were read and agreement was achieved by consensus.

Data Extraction

Data extraction was performed by 1 investigator (BL) using a standardized data extraction form. The following data were extracted from each study: (1) first author, year of publication, location of study, (2) study design, (3) sample size, (4) characteristics of the adult-onset and childhood-onset patients (mean age at symptom or study onset, mean disease duration, mean length of follow-up), (5) autoantibody profiles and laboratory tests (expressed as either the number or the percentage of adult-onset and childhood-onset patients), (6) mean SLEDAI and SDI scores. Several studies presented data for 3 age groups: childhood-onset, adult-onset, and older/elderly-onset. Data for older-onset lupus were not extracted if there were child-onset, adult-onset, and older-onset groups all given within an article, so that childhood-onset was compared to adult-onset but not elderly-onset. The studies were not blinded to the abstractor and, where there was uncertainty around data within an article, then consensus was reached by an independent review from both BL and JP.

Quality Assessment

Study quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort, case-control, and cross-sectional studies (combined) (13). The STROBE checklist consists of 22 items; however, 4 items are specific to cohort, case-control, or cross-sectional studies. The maximum score varies based on the number of applicable items on the checklist. One item on the checklist (16c), pertaining to translating estimates of relative risk into absolute risk for a meaningful time period, was not relevant to any of the articles. One item applied only to matched studies (6b), and another item applied only to cohort studies (14c). The maximum attainable score ranged from 31 to 33.

Statistical Analysis

For the autoantibodies and laboratory tests data, the raw numerical data (event rates) were extracted from the studies and the odds ratios (OR) or relative risks (RR) were recalculated. For SLEDAI and SDI data, the sample sizes, mean scores, and standard deviations were recorded. If a study reported data for more than 1 time point (eg, at disease onset and during evolution), data from the most recent time point were extracted. Extracted data were used for combining studies for each autoantibody, test result, or disease score of interest using forest plots. In some instances, several related variables were combined into 1 forest plot (eg, IgG and IgM anticardiolipin antibody). If a study reported data for more than one of the variables included in the forest plot, the highest event rate was taken.

For the autoantibody and laboratory test data, the random effects model described by DerSimonian and Laird was used to calculate the pooled ORs (14). In this model, the weight of the study is proportional to the inverse of the within-study variance via the Mantel-Haenszel weighting technique for ORs. This was used in preference to the