Neuropsychiatric Syndromes in Systemic Lupus Erythematosus: A Meta-Analysis

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Objectives: To assess the prevalence of the 19 neuropsychiatric (NP) syndromes in systemic lupus erythematosus (SLE) patients, as defined by the American College of Rheumatology (ACR) in 1999, and better understand the reasons for interstudy variability of prevalence estimates, by performing a meta-analysis of relevant publications.

Methods: A literature search from April 1999 to May 2008 was performed to identify studies investigating NP syndromes in patients with definite SLE, applying the 1999 ACR case definitions and having a sample size of at least 30 patients. Excluded were studies that did not relate to all 19 NPSLE syndromes, presented duplicate data, or were irrelevant.

Results: Seventeen of 112 identified studies matched the inclusion criteria, reporting on a total of 5057 SLE patients, including 1439 NPSLE patients, with 2709 NPSLE syndromes. In a subanalysis of the 10 higher quality prospective and elicited studies (2049 patients) using the random-effects model, the prevalence of NP syndromes in SLE patients was estimated to be 56.3% (95% CI 42.5%-74.7%), and the most frequent NP syndromes were headache 28.3% (18.2%-44.1%), mood disorders 20.7% (11.5%-37.4%), cognitive dysfunction 19.7% (10.7%-36%), seizures 9.9% (4.8%-20.5%), and cerebrovascular disease 8.0% (4.5%-14.3%), although significant between-study heterogeneity was present ($P < 0.05$). Autonomic disorder and Guillain-Barré syndrome carried a prevalence of less than 0.1%. No case of plexopathy was reported.

Conclusions: NP syndromes were estimated to exist in more than half of SLE patients. The most prevalent manifestations were headache, mood disorders, and cognitive dysfunction. A major limitation of the study was the significant heterogeneity of prevalence estimates between studies.

Semin Arthritis Rheum 41:1-11

Keywords: *meta-analysis, prevalence, neuropsychiatric, systemic lupus erythematosus, American College of Rheumatology*

Neuropsychiatric manifestations are commonly found in patients with SLE and are an important cause of morbidity and mortality in these patients (1). However, for many years, lack of consensus in defining neuropsychiatric syndromes in systemic lupus erythematosus (NPSLE) presented a major obstacle in their research. In 1999, the American College of Rheumatology (ACR) Ad Hoc Committee on neuropsychiatric lupus nomenclature developed case definitions for 19 NPSLE syndromes to standardize definitions, diagnostic criteria, exclusions, associations, and diagnostic testing (2). Since its publication in 1999, this nomenclature has been widely accepted and many studies have investigated the prevalence of the 19 neuropsychiatric (NP) syndromes in both adult and pediatric SLE populations. Despite using these standardized definitions, the prevalence of NP manifestations in SLE patients has ranged widely from 12 to 95% in different series (3-19). This vast interstudy difference was previously attributed to multiple factors, including study design (prospective vs retrospective),

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0049-0172/11/$-see front matter
doi:10.1016/j.semarthrit.2010.08.001

diverse screening strategies used across studies, different baseline characteristics of the patients (adult vs pediatric patients, disease duration, disease severity, ethnicity etc), and duration of follow-up (1). Hence, the overall prevalence of NPSLE is currently unclear.

A decade after the first publication of the 1999 ACR case definitions, we conducted a meta-analysis of relevant studies that assessed the prevalence of NPSLE by employing these case definitions. Our goals were to estimate the overall prevalence of NPSLE; evaluate the relative prevalence of each of the 19 NP syndromes, with special attention to the rare syndromes that are not represented in most series; and better understand the reasons for the marked variance of prevalence estimates between studies.

METHODS

This study was conducted according to the guidelines outlined by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (20).

Data Sources and Searches

We conducted a PubMed/Medline and EMBASE search from April 1999 to May 2008 utilizing the following commonly used keywords: 'neuropsychiatric' and 'lupus' or 'CNS' and 'lupus,' combined with 'American College of Rheumatology' or 'ACR.' A follow-up of the relevant bibliography in articles was also undertaken to identify additional relevant articles. In certain cases, we corresponded with the authors of the articles for further information or clarification.

Study Selection

Abstracts of all identified reports published in all languages were reviewed independently by 2 investigators (A.U. and J.N.). Case reports, review articles, and papers not dealing with SLE patients were excluded and were not further reviewed. In case an abstract was considered potentially relevant by either 1 of the 2 investigators, the article was reviewed in full-text and assessed for relevance by applying a checklist of inclusion and exclusion criteria. Included were studies investigating NP syndromes in patients with definite systemic lupus erythematosus (SLE) (ie, each patient fulfilling at least 4 ACR criteria for SLE), applying the 1999 ACR case definitions, and having a sample size of at least 30 patients. Excluded were studies that did not relate to all 19 NPSLE syndromes, studies that presented duplicate data, or irrelevant studies that were not identified in the initial review of abstracts (eg, case reports or review articles).

Data Extraction and Quality Assessment

For each relevant study, we identified and recorded the total number of SLE patients, the number of NP patients, the cumulative number of NP syndromes (each patient could have more than 1 NP syndrome during the course of the disease), the study design and characteristics of patients, including age group (adult or pediatric), mean age, disease duration, age at SLE diagnosis, gender distribution, ethnicity, and nationality. We also recorded the cumulative prevalence of each of the 19 NPSLE syndromes in each cohort, as well as the SLE Disease Activity Index and the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index when available. When possible, we extracted the exact numbers of syndromes as reported in the articles, and when not available we calculated them from proportions provided. The process of data extraction was performed by a single investigator (A.U.) to assure uniformity of the data and then re-evaluated by a second investigator (J.N.).

Data Synthesis and Analysis

Prevalence estimates for each of the 19 NP syndromes and the total NPSLE prevalence for each study were calculated together with their 95% confidence intervals (CI). Additionally, prevalence rates for prospective or elicited, and separately, retrospective studies were estimated with 95% CI and an overall prevalence rate with 95% CI was also calculated. Except where indicated otherwise, prevalence rates are shown as percentage of the entire SLE patient population. Comparison of the prevalence estimates of each of the 19 NP syndromes between prospective/elicited and retrospective studies was conducted using the χ^2 test. Tests were 2-sided and considered significant at $P < 0.001$ to account for multiple comparisons and maintain the overall alpha level at approximately 5%. Because of the significant difference in reported prevalence between these 2 types of studies, between-study heterogeneity of each NP syndrome was assessed only for the prospective/elicited studies, using the χ^2 test ($P < 0.05$ indicating significant heterogeneity) and the Higgins and Thompson's heterogeneity index (21).

In addition to arithmetic means, prevalence estimates were combined across prospective/elicited studies, using both fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian-Laird) models (22-24). Random-effects models tend to provide wider confidence intervals (24) and are preferable in the presence of between-study heterogeneity. Except where otherwise indicated, random-effects estimates are displayed.

Statistical calculations were done with WinPepi software version 7.4 (25) and with Microsoft Excel 2003.

RESULTS

Our search identified 112 articles (Fig. 1), of which 17 met the inclusion criteria and were incorporated in the final analysis (Table 1). The final cohort comprised of 5057 SLE patients. Of these, 1439 patients (28.5%, range: 12.2%-94.7%) had 2709 NP syndromes (mean of 1.88 syndromes per NPSLE patient, range: 1.0-3.48).