Risk of ischemic stroke in patients with systemic sclerosis: A systematic review and meta-analysis

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Abstract

Background. Several chronic inflammatory disorders, such as rheumatoid arthritis and idiopathic inflammatory myositis, have been shown to increase risk of ischemic stroke but the data on systemic sclerosis (SSc) remains unclear.

Methods. We conducted a systematic review and meta-analysis of observational studies that reported odds ratio, relative risk, hazard ratio, or standardized incidence ratio comparing risk of ischemic stroke in patients with SSc versus non-SSc participants. Pooled risk ratio and 95% confidence intervals (CIs) were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird.

Results. Four retrospective cohort studies were identified and included in our data analysis. We found a statistically significant elevated ischemic stroke risk in patients with SSc with a pooled risk ratio of 1.68 (95% CI, 1.26–2.24). The statistical heterogeneity was moderate with an I² of 69%.

Conclusions. Our study demonstrated a statistically significant increased ischemic stroke risk among patients with SSc.

Introduction

Over the past few decades, several large epidemiological studies have demonstrated an increased incidence of cardiovascular disease among patient with chronic inflammatory disorders, such as rheumatoid arthritis, idiopathic inflammatory myositis, vasculitis, systemic lupus erythematosus and autoimmune liver diseases [1–6]. Premature atherosclerosis from chronic inflammation appears to be the cornerstone of these excessive cardiovascular complications [7–9].

Systemic sclerosis (SSc) is another autoimmune connective disease characterized by diffuse fibrosis of the skin and internal organs. Its incidence varies from 0.6 per million person-year to 122 per million person-year [10]. SSc is subcategorized into diffuse and limited form, based on the extent of skin involvement. The pathogenesis of this disorder is complex and not well understood. Microvascular abnormality is one of the hallmarks of its pathology which is linked to the clinical presentations of Raynaud’s phenomenon, periungual capillary changes, gastric antral vascular ectasia, and scleroderma renal sclerosis [11].

Though not originally regarded as a clinical feature of SSc, macrovascular complication has been increasingly recognized in this group of patients as a possible link to coronary artery disease (CAD), and this autoimmune disorder has been suggested in several case reports [12,13]. Subsequent epidemiological studies and a meta-analysis have confirmed this association with an overall 82% excess risk compared with sex- and age-matched controls [14–16].

Ischemic stroke is another major atherosclerotic macrovascular disease that shares a similar pathogenesis to CAD. Patients with SSc might be at an increased risk of ischemic stroke as well. Nonetheless, these data remain inconclusive as previous epidemiological studies yielded inconsistent results [17–19]. Thus, to further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the ischemic stroke risk in patients with SSc versus non-SSc participants.

Methods

Search strategy

Two investigators (P.U. and A.S.) independently searched published studies indexed in MEDLINE and EMBASE from inception to February 2015 using the terms for SSc combined with the terms for ischemic stroke. Detailed search strategy is available in Supplementary data available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1056931. References of selected retrieved articles were also manually searched.

Inclusion criteria

The inclusion criteria were as follows: (1) Population-based, case–control, or cohort studies published as original study or abstract to evaluate the risk of incident ischemic stroke in patients with SSc; (2) odds ratio (OR), relative risk (RR) or hazard ratio (HR), or standardized incidence ratio (SIR) with 95% confidence
intervals (CIs) or enough data to calculated these ratios were provided (3). Participants without SSc were used as the reference group in cohort study and participants without ischemic stroke were used as the reference group in case–control study.

Study eligibility was independently determined by the two investigators noted above. Any differences in decision were resolved by consensus with the third investigator. The quality of each study was also independently assessed by each investigator using Newcastle–Ottawa quality assessment scale [20].

**Data extraction**

A standardized data collection form was used to extract the following information: last name of the first author, title of the article, study design, year of publication, country of origin, number of case and control, control selection, characteristics of included participants, method used to diagnose SSc and ischemic stroke, average duration of follow-up, confounders, and adjusted effect estimates with 95% CI. This data extraction was performed by all three investigators. Any discrepancy in data extraction was also resolved by consensus.

**Statistical analysis**

Review Manager (RevMan) 5.3 software from the Cochrane Collaboration was used for the statistical analysis. Point estimates and the corresponding standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird [21]. We used a random-effect model rather than a fixed-effect model, in light of the high likelihood of between study variance. Cochran’s Q test was used to determine the study’s statistical heterogeneity. This statistic is complemented with the I² statistic, which quantifies the proportion of total variation across studies that is due to true heterogeneity rather than chance. A value of I² of 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and >75% high heterogeneity [22].

**Results**

Our search strategy yielded 209 potentially relevant articles (78 from Medline and 131 articles from EMBASE). After exclusion of 75 duplicated articles, 134 articles underwent title and abstract review. 124 articles were excluded as they clearly did not fulfill our inclusion criteria. Four studies, all of which were retrospective cohorts, with 5,097 patients with SSc met our inclusion criteria and were included in the data analysis [17–19,24]. The search methodology and literature review process are outlined in Figure 1. The detailed characteristics and Newcastle–Ottawa scale of the included studies are illustrated in Table 1.

We found a statistically significantly elevated risk of ischemic stroke in patients with SSc versus control with the pooled risk ratio of 1.68 (95% CI, 1.26–2.24). The statistical heterogeneity was moderate with an I² of 69%. Figure 2 demonstrates the forest plot of the included studies.

**Sensitivity analysis**

To further explore the statistical heterogeneity, we performed a sensitivity analysis by excluding the study by Zöller et al. [18] as this study was the only study that included only hospitalized patients, which could potentially lead to a selection of only severe cases. This sensitivity analysis considerably reduced the I² to 51% without significantly altering the pooled risk ratio (RR, 1.88; 95% CI, 1.43–2.48).

**Evaluation for publication bias**

Funnel plot (Figure 3) was used for the evaluation for publication bias. The plot was asymmetric, suggesting that publication bias in favor of positive studies might be present.

**Discussions**

Our meta-analysis demonstrated a significant association between SSc and ischemic stroke with an overall 1.68-fold (95% CI, 1.26–2.24) increased risk compared with non-SSc participants. The increased risk of ischemic stroke was consistently seen across all studies, with the exception of Zöller et al, in which the increased risk was numerically evaluated but not statistically significant. [18].

Why patients with SSc have an increased risk of cerebrovascular events is not well understood. Premature atherosclerosis related to chronic inflammation is the widely accepted hypothesis as the deleterious effects of inflammatory mediators and oxidative stress on endothelial function have been extensively documented [7–9,25]. In fact, increased atherosclerotic burden in patients with SSc has been demonstrated in several studies [26–28]. In addition, chronic inflammation related to autoimmune disorder is known to cause a hypercoagulable state as inflammatory cytokines have been shown to promote the coagulation cascade, inhibit the anti-coagulation pathway and impair the fibrinolytic process [29–31]. These factors, in conjunction with the vasculopathy of SSc may serve as the fundamental pathophysiology of the development of ischemic stroke.

Even though the included studies were of high quality, there are some limitations and, therefore, our results should be interpreted with caution. First, all of the included studies were medical registry-based studies. Thus, coding inaccuracies and incompleteness for both SSc and ischemic stroke may have been...
Table 1. Main characteristics of studies included in the meta-analysis.

| Country       | Study design          | Year   | Cases                                             |
|---------------|-----------------------|--------|---------------------------------------------------|
| Sweden        | Retrospective cohort  | 2012   | All hospitalized patient with a diagnosis of SSc |
|               |                       |        | (without previous or co-existing ischemic stroke) |
|               |                       |        | between 1987 and 2008. Cases were identified   |
|               |                       |        | from the Swedish national registry.            |
| Taiwan        | Retrospective cohort  | 2013   | All patients who were newly diagnosed with SSc    |
|               |                       |        | between 1995 and 2006. Cases were identified    |
|               |                       |        | using The National Health Insurance Network      |
|               |                       |        | database which provided comprehensive health    |
|               |                       |        | care for all citizens of Taiwan. Cases           |
|               |                       |        | with previous diagnosis of stroke were          |
|               |                       |        | excluded.                                        |
| United Kingdom| Retrospective cohort  | 2012   | All patients who were newly diagnosed with SSc    |
|               |                       |        | between 1996 and 2010. Cases were identified     |
|               |                       |        | using the comprehensive provincial medical       |
|               |                       |        | services plan database.                         |

Diagnosis of SSc
- Diagnostic code from the registry.
- Swedish age- and sex-specific general population incidence rates for ischemic stroke were used as the comparator for the calculation of standardized incidence ratio.
- Diagnosed from the same database.
- Sex- and age-matched subjects randomly selected from same database.
- Age, sex, and month/year of cohort entry-matched subjects randomly selected from same database.
- Sex, age, and co-morbidities.
- Age, sex, time of cohort entry, comorbidities, NSAIDs and steroid use.

Controls
- Subjects randomly selected from the same database.
- Subjects randomly selected from the same database.
- Diagnosis of ischemic stroke.
- Age, socioeconomic status, region of residence, obesity, HTN, diabetes, atrial fibrillation, heart failure, and coronary heart disease.
- Age, sex, and co-morbidities, and medications.

Follow-up
- Until the stroke, death, emigration from the system or September 30, 2011.
- Until the stroke, death, emigration from the system or December 31, 2008.
- Until hospitalization for stroke, death, emigration from the system or December 31, 2008.
- Until the stroke, death, or December 31, 2006.
- NA

Quality assessment (Newcastle-Ottawa scale)
- Selection: 4 stars
- Comparability: 2 stars
- Outcome: 3 stars
- Selection: 4 stars
- Comparability: 1 star
- Outcome: 3 stars
- Selection: 4 stars
- Comparability: 2 stars
- Outcome: 3 stars
- Selection: 3 stars
- Comparability: 2 stars
- Outcome: 3 stars

SSc: systemic sclerosis, NA: not available, HTN: hypertension, NSAIDs: non-steroidal anti-inflammatory drugs.

present. Second, we could not evaluate the risk of each subtype of SSc (i.e., diffuse and limited SSc) as the primary studies did not provide data for each subgroup. Third, statistical heterogeneity was present in this meta-analysis, though the I² square considerably decreased after excluding the study with potential selection bias [18]. Fourth, as previously discussed, publication bias in favor of positive studies might be present. Fifth, this is a meta-analysis of observational studies which, at best, can demonstrate only an association, not causality. Therefore, we cannot be certain that SSc itself or other potential confounders were responsible for the increased risk. Furthermore, detection bias might have been present in these studies as the patients in SSc cohort, because of their chronic illness, were exposed to more medical examinations and investigations and, thus, more likelihood of stroke detection [32].

In conclusion, our meta-analysis demonstrated a statistically significant increased ischemic stroke risk among patients with SSc with 68% excess risk. Physicians should be aware of this association, and a strategy to control other traditional cardiovascular risk factors should be employed as a part of standard of care for these patients.

Authors’ contributions
All authors had access to the data and a role in writing the manuscript.
Figure 3. Funnel plot of the included studies.

P. Ungprasert: Concept and design, performing the search, analysis, and interpretation of data, critical writing of the intellectual content, and final approval of the version to be published.

A. Sanguankeo: Performing the search, analysis, and interpretation of data, critical writing of the intellectual content, and final approval of the version to be published.

S. Upala: Analysis of data, critical revising of the intellectual content, and final approval of the version to be published.

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Conflict of interest
None.

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Supplementary material available online
Supplementary Questionnaire.