Letters

RESEARCH LETTER

Autoantibodies Present Before Symptom Onset in Primary Sjögren Syndrome

Autoantibodies are characteristic of primary Sjögren syndrome[1] and may be involved in its pathogenesis.[2] We investigated autoantibodies present before symptom onset in patients with Sjögren syndrome because data on this issue are limited.

Methods | All patients with primary Sjögren syndrome at Malmö University Hospital (Malmö, Sweden) have been included in a registry since 1984.[3] To obtain presymptomatic serum samples, the registry was linked with 3 biobanks containing specimens from 625 000 individuals submitted for microbiological analyses or population-based studies of healthy individuals.[4]

Date of symptom onset was determined retrospectively from the patient during the first office visit at which Sjögren syndrome was diagnosed. All cases provided written informed consent at inclusion in the registry. The study was approved by the ethics committee at Lund University.

All patients with available samples who met consensus criteria for Sjögren syndrome[1] were included. When multiple samples were available for a single patient, the earliest positive sample was used. Controls were randomly selected from the biobanks and matched by sex, age, and date of earliest sampling (within 60 days before or after) to each case. None of the controls were diagnosed with Sjögren syndrome. Those serum samples that were obtained from the microbiology biobank had been submitted due to symptoms unrelated to Sjögren syndrome (eg, pregnancy screening, suspected influenza). Samples were collected from 1976 through 2001 and Sjögren syndrome was diagnosed through 2011.

Autoantibodies against Ro60/SSA, Ro52/SSA, La/SSB, Sm, RNP, Scl-70, Jo-1, ribosome P, and chromatin were detected using a multiplex immunobead assay (QUANTA Plex SLE Profile 8, INOVA Diagnostics) and analyzed on a Luminex 100 instrument (Luminex Corp). Antinuclear antibodies (ANAs) were analyzed by immunofluorescence with HEp-2 cells as the antigens. Immunoglobulin M-class rheumatoid factor (RF) was analyzed with an in-house enzyme-linked immunosorbent assay.

Descriptive statistics and a 2-sided Friedman test were used for statistical analysis (Statistics version 20.0; IBM SPSS). $P < .05$ was considered statistically significant.

Results | Of 360 cases in the registry, 44 (41 women and 3 men; mean [SD] age, 53 [13] years [range, 25-78 years] at symptom onset) provided 64 presymptomatic serum samples obtained a mean (SD) of 7 (5.5) years (range, 1-23 years) before symptom onset. They were representative of the whole registry cohort based on age, sex, and disease severity (eg, positive salivary gland biopsy, postdiagnostic presence of anti-Ro/SSA and anti-La/SSB antibodies, and systemic involvement).

The mean duration between symptom onset and the first office visit was 3.7 (median, 3.0) years. Forty-four controls (41 women and 3 men; mean [SD] age, 53 [13] years) provided 44 serum samples.

In 29 cases (66%), autoantibodies were detected before symptom onset (primarily ANA, followed by RF, anti-Ro60/SSA, anti-Ro52/SSA, and anti-La/SS-B; **Table** and **Figure**). All 29 cases had autoantibodies in their earliest available serum sample, as early as 18 years before symptom onset (median, 5 [interquartile range {IQR}, 3.0-7.5] years for ANA, 6 [IQR, 3.0-13.0] years for RF, 4 [IQR, 2.25-7.75] years for antibodies against Ro60/SSA, 5 [IQR, 3.0-8.0] years for antibodies against Ro52/SSA, and 4 [IQR, 2.75-9.0] years for antibodies against La/SSB).

There was no statistically significant difference in the time between a positive test result and symptom onset between autoantibodies ($P = .41$). The odds ratio (OR) for developing Sjögren syndrome was high for both anti-Ro60/SSA (OR, 15.0; 95% CI, 1.9-118.5) and anti-La/SSB (OR, 10.0; 95% CI, 1.2-81.5) antibodies (Table). For anti-Ro52/SSA, none of the controls vs 15 cases were reactive.

Discussion | To our knowledge, this is the first systematic investigation of presymptomatic autoantibodies in Sjögren syndrome. Most cases produced autoantibodies many years before clinical onset of the disease; the median time of 4 to 6 years is an underestimate because all seropositive cases had autoantibodies in their earliest available serum sample.

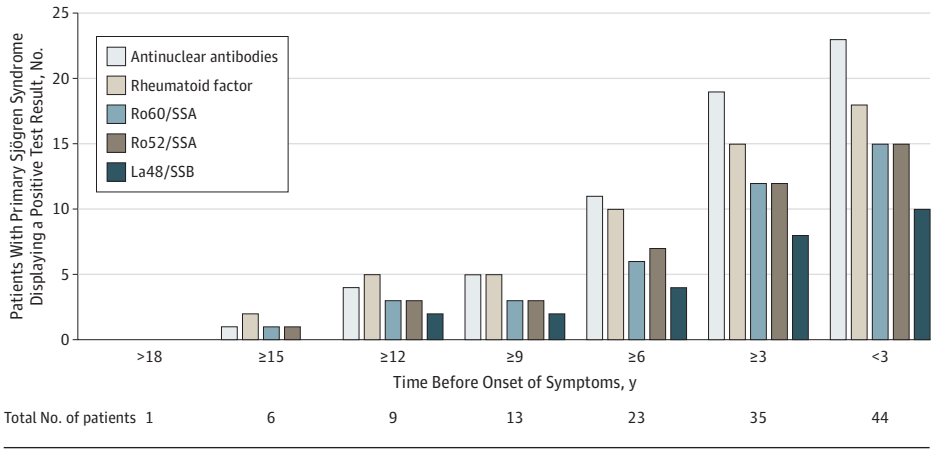
Table. Presence of Autoantibodies Before Symptom Onset in 44 Patients With Primary Sjögren Syndrome and 44 Matched Controls[a]

Type of Autoantibody	No. (%) of Patients With a Positive Presymptomatic Test Result (n = 44)	Time Between a Positive Test Result and Symptom Onset, Median (Range), y	No. (%) of Controls With a Positive Test Result (n = 44)	Odds Ratio (95% CI)
Antinuclear antibodies	23 (52)	5 (1-18)	4 (9)	5.8 (1.8-18.0)
Rheumatoid factor	18 (41)	6 (1-18)	4 (9)	4.5 (1.4-14.4)
Anti-Ro60/SSA	15 (34)	4 (1-18)	1 (2)	15.0 (1.9-118.5)
Anti-Ro52/SSA	15 (34)	5 (1-18)	0	NA[b]
Anti-La/SSB	10 (23)	4 (1-14)	1 (2)	10.0 (1.2-81.5)

[a] Serum samples were obtained from the Southern Sweden Microbiology Biobank and 2 biobanks established during the projects (Malmö Preventive Medicine and Malmö Diet and Cancer).[4] Anti-RNP and antichromatin antibodies were detected in 1 patient each (2%). None of the patients were positive for autoantibodies against Sm, Scl-70, Jo-1, or ribosome P.

[b] Not applicable because none of the controls were reactive.

Figure. Cumulative Number of Patients With Primary Sjögren Syndrome With Autoantibodies Before Clinical Onset



A limitation of the study is the wide confidence intervals that reflect the small sample size and may indicate unstable estimates. Also, we cannot eliminate the possibility that seropositive controls may have had undiagnosed Sjögren syndrome (3-11 years diagnostic delay has been reported)[5,6] or may develop the disease in the future.

Autoantibody profiling may identify individuals at risk many years before disease onset. However, the significance of these presymptomatic autoantibodies for determining prognosis and treatment remains to be determined.

Roland Jonsson, DMD, PhD
Elke Theander, MD, PhD
Bitte Sjöström, MSc
Karl Brokstad, PhD
Gunnel Henriksson, MD, PhD

Author Affiliations: Broegelmann Research Laboratory, University of Bergen, Bergen, Norway (Jonsson, Brokstad); Department of Rheumatology, Lund University, Malmö, Sweden (Theander); Department of Laboratory Medicine Malmö, Lund University, Malmö, Sweden (Sjöström, Henriksson).

Corresponding Author: Gunnel Henriksson, MD, PhD, Lund University, Jan Waldenströms St 59, 20502 Malmö, Sweden (gunnel.henriksson@med.lu.se).

Author Contributions: Dr Henriksson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Jonsson and Theander contributed equally to the article.
Study concept and design: Jonsson, Theander, Henriksson.
Acquisition of data: Jonsson, Theander, Sjöström, Brokstad, Henriksson.
Analysis and interpretation of data: Jonsson, Theander, Sjöström, Brokstad, Henriksson.
Drafting of the manuscript: Jonsson, Theander, Brokstad, Henriksson.
Critical revision of the manuscript for important intellectual content: Jonsson, Theander, Sjöström, Brokstad, Henriksson.
Statistical analysis: Theander, Sjöström.
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COMMENT & RESPONSE

Acute Ischemic Stroke and Timing of Treatment

To the Editor Dr Saver and colleagues[1] used the Get With The Guidelines-Stroke (GWTG-Stroke) registry to investigate the association of time to tissue-type plasminogen activator