Relationship between silent brain infarction and rheumatic diseases

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Abstract
Aim: Silent brain infarction (SBI) is a vascular disease without any clinical symptoms that is detected in brain imaging. The diagnosis of SBI vary according to the SBI identification and imaging method used. Inflammatory diseases and treatments may cause SBI at an early age because of the increased risk of thrombosis. We aimed to determine the relationship between cranial lesions and rheumatologic disease. Material and Method: Data were obtained from the clinical files of 4560 patients who were between 20 and 60 years of age, applied to the neurology out-patient clinic between January 2013 and December 2015 and had cranial magnetic resonance imaging (MRI). The Fazekas scale was used to define the load and location of the lesions. Patients over 60 years of age, younger than 20 years, with hypertension, diabetes mellitus, hyperlipidemia, previous cerebrovascular disease, white matter lesion consistent with demyelinating disease, or large vessel occlusion were excluded. Results: SBI was detected in 254 (5.5%) patients. Connective tissue disease in 13 patients, rheumatoid arthritis in 9 patients, Behçet’s disease in 6 patients, anti-phospholipid syndrome in 2 patients and other rheumatic diseases in 3 patients were detected. There was no statistically significant difference between the groups with and without rheumatologic disease in terms of lesion load and localization. There was a positive correlation between age and lesion load. Discussion: Brain MRI findings alone are inadequate in diagnosing SBI without clinical findings and specific laboratory indicators for the patients.

Keywords
Magnetic Resonance Imaging; Silent Brain Infarction; Rheumatologic Diseases
Introduction
Due to the better quality of imaging modalities and the increasing frequency of their use, many situations that are not detected by the clinical status of the patients are being diagnosed. Lesions incidentally detected by brain magnetic resonance imaging (MRI) are basically classified into 3 groups as: vascular, neoplastic and non-neoplastic cystic lesions. Silent brain infarction (SBI) is a vascular disease without any clinical symptoms that is detected in brain imaging [1]. The diagnosis of SBI vary according to the SBI identification and imaging method used. In studies, the prevalence of SBI in healthy populations has been found to be 8-28%. Comorbid diseases, age, and ethnicity are factors that increase the frequency of SBI [2]. A strong correlation between SBI and stroke has been shown. At the same time, 5-year follow-up of patients with SBI has shown that cognitive function loss is two times greater compared to those with normal MRI findings. The number and location of the lesions are closely related to the loss of cognitive function and stroke. Therefore, in some studies, these clinically unrecognized lesions are defined as “occult” rather than “silent” brain infarction [3, 4].

In rheumatologic diseases, the risk of thrombosis and ischemia are greater and emerge in earlier years than in the normal population. Comorbid diseases which are known to be risk factors for ischemia and thrombosis, such as vasculitis, anti-phospholipid syndrome, and hypertension may be associated with rheumatic diseases. It is also known that inflammation causes ischemic events by increasing the risk of atherosclerosis. In rheumatic diseases, atherosclerosis occurs at an earlier age and faster than normal. This is caused by the cytokine storm that occurs in inflammation. Increased levels of serum C-reactive protein (CRP) produced in response to tumor necrosis factor (TNF) and of interleukin-6 have been shown to be independent risk factors for myocardial infarction and stroke. Besides CRP levels, TNF may activate endothelial cells and produce a procoagulant-prothrombotic state. TNF is a cytokine that plays a key role in the development of ischemic tolerance and repair of ischemia and in the onset and progression of stroke pathogenesis. Finally, drugs especially used in immunosuppressive treatments, may increase the risk of ischemia [5, 6].

In this study we aimed to determine the relationship between cranial lesions and rheumatologic disease in patients who had cranial MRI ischemic lesions without any clinical signs.

Material and Method
Our study was a hospital-based retrospective study. Data were obtained from the clinical files of 4560 patients who were between 20 and 60 years of age, applied to the neurology out-patient clinic between January 2013 and December 2015 and had a cranial MRI. Cranial Images were obtained using 1.5 Tesla MR (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany). SBI was defined as 3 mm and larger lesions using T2 weighted and FLAIR images. Patients with SBI were reassessed by the same radiologist. SBI lesions were classified as periventricular, subcortical, or deep white matter lesions. The Fazekas scale was used to define the load and location of the lesions. It was used to measure the burden of white matter T2 hyperintense lesions, mostly attributed to chronic small vessel ischemia. A grade was given depending on the size and confluence of the lesions. Lesions were rated as 0=absence, 1=“caps” or pencil-thin lining, 2=smooth “halo,” or 3=irregular white matter hyperintensity extending into the deep white matter [7]. Patients over 60 years of age, younger than 20 years, with hypertension, diabetes mellitus, hyperlipidemia, previous cerebrovascular disease, white matter lesion consistent with demyelinating disease, or large vessel occlusion were excluded. Serum creatinine, total cholesterol, low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), triglyceride (TG), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), uric acid, alanine aminotransferase (ALT), hemogram, homocysteine, thyroid stimulating hormone (TSH), antinuclear antibody (ANA) and anti-phospholipid antibodies and venous blood fasting glucose level (FBG) were measured in SBI patients after 8 hours of overnight fasting. The ANA test was performed using the indirect immunofluorescence (IIF) method using the Hep-2 cells, the measurement of FBG, creatinine, ALT, LDL-C, HDL- ESR were done using the enzymatic method with the Beckman AU 5800 Autoanalyzer (Beckman Coulter Inc., USA) and ESR was measured with an automated Alifax THL1 instrument (Alifax SPA, Padua, Italy). Lupus-anticoagulant (LA), anticardiolipin (aCL) ELISA and anti-β2-glycoprotein-I ELISA tests were used for anti-phospholipid antibody detection. The clinical evaluation and laboratory testing of the patients diagnosed with SBI were done by the same rheumatologist. Ethics Committee approval for this study protocol was obtained.

The statistical analysis program SPSS version 20.0 (IBM Corp., Armonk, New York, USA) was used for statistical analysis. Descriptive statistics were presented as frequency, percent, mean and standard deviation. The confidence interval of the study was 95%. The single-sample Kolmogorov-Smirnov test, a nonparametric test, was used to determine whether the results of the groups fit the normal distribution. For analysis of differences between two groups of continuous variables, the Mann-Whitney U test was used when the data distribution was abnormal, and the Student t test was used when it was normal. A P value of less than 0.05 was considered statistically significant.

Results
In our study, SBI was detected in 254 (5.5%) patients. Rheumatic diseases were detected in 33 patients, connective tissue disease in 13 patients, rheumatoid arthritis in 9 patients, Behçet's disease in 6 patients, anti-phospholipid syndrome in 2 patients and other rheumatic diseases in 3 patients. The mean age of the patients diagnosed with rheumatic disease was 44 ± 10.3 years and the mean age of the group without rheumatic disease was 44.6 ± 10.3 years. There was no statistically significant difference between the two groups. There were 28 (84.8%) women in the SBI group and 140 (63.3%) women in the non-SBI group, with a significant gender difference between the two groups (p = 0.01). There was no difference between the two groups in terms of the laboratory test results. The laboratory data of the patients are presented in Table 1. When the patients were classified according to the lesion location, periventricular lesions were detected in 13 (59.4%) patients, subcortical...
lesions in 16 (48.5%) patients and deep white matter lesions in 4 (12.1%) patients with rheumatic disease. Of the patients without rheumatic disease, 85 patients (38.5%) were found to have periventricular SBI, 134 (60.6%) had subcortical SBI, and 2 (0.9%) had SBI localized to deep white matter. The percentage of patients with periventricular lesions was statistically similar in patients with and without rheumatic disease. Subcortical lesions were more frequent in the group without rheumatic disease, but no statistical significance was found. Deep white matter lesions were more frequent in patients with rheumatic diseases compared to the non-rheumatic group (p = 0.003) (Table 2). When the patients were assessed by the Fazekas scale according to the amount of lesions, grade 1 disease was found in 22 (66.7%); grade 2 disease was found in 9 (27.3%); and grade 3 disease was found in 2 (6.1%) with rheumatic disease. In the group without rheumatic disease grade 1 disease was found in 117 (53.4%); grade 2 disease was found in 86 (39.3%); and grade 3 disease was found in 16 (7.3%). There was no statistically significant difference between the groups with and without rheumatologic disease in terms of lesion load (Table 3).

Discussion
In this study, there was no significant relationship between the presence of rheumatologic disease, lesion location and amount of lesions in patients with SBI. Only deep white matter lesions were found to be statistically significantly more frequent in the patients with rheumatic disease. However, the low number of patients in this group does not permit a conclusion that ‘deep white matter lesions are more common in rheumatic diseases’. SBI is defined as ischemic events that do not present any clinical signs and are detected in imaging modalities. The frequency of detection of these lesions increases with the improvement of imaging modalities. Age is considered to be an important risk factor that increases the incidence of SBI. In a study conducted by Russo et al., SBI frequency was found to be 15.4% in 455 subjects with an average age of 70 [8]. Vermeer et al. detected the frequency of SBI to be 20% in their population-based Rotterdam Scan study in which 1077 subjects with a mean age of 72 participated [9]. In studies enrolling younger participants, SBI frequency was found to be 5% [10, 11]. While a frequency range of 10-20% was determined in community samples studies, a larger frequency interval is detected in routine health screening studies [12, 13, 14, 15, 16]. In our study, the frequency of SBI was detected to be 5.5% in patients aged 20-60 years. In our study, participation of younger subjects and exclusion of significant risk factors such as hypertension and diabetes mellitus may have caused the frequency of SBI to be lower than in other studies. The frequency of SBI and rheumatic disease in our study was more common in females. SBI was more frequent in females in a Rotterdam scan study, but the difference was not statistically significant [9, 17]. Most of the studies in the literature have not identified gender differences in frequency of SBI lesions [18, 19, 20]. The pathophysiology of SBI is not clearly known. It is thought to be caused by mechanisms similar to those of cerebrovascular diseases. Endothelial dysfunction, atherosclerosis, and oxidative stress, which are common in rheumatologic diseases, are among the possible contributing mechanisms [21]. There are no studies about the frequency and location of SBI in rheumatologic diseases in the literature. In our study, SBI was seen more frequently in the subcortical area, but no significant relationship was found between rheumatic diseases and SBI. Patients with deep white matter lesions were more likely to have rheumatic disease. However, the low number of patients suggests that the statistical power is insufficient and does not constitute clinical significance. In a study of Delgado et al. that enrolled hypertensive patients, SBI lesions were detected at 28.8% in subcortical white matter and 35.6% in deep white matter regions [22]. In a study investigating the relationship between SBI and depression, SBI was found to be statistically significantly higher in basal ganglia of the patients with depression [23]. In the literature, there are similar studies about the relationship between SBI and various diseases, but there is no ischemic

Table 1. Demographic and laboratory data of study groups

| Parameters | Patient with rheumatic disease (n=35) | Patient without rheumatic disease (n=221) | p |
|------------|-------------------------------------|------------------------------------------|---|
| Age (SD, years) | 44±10.3 | 44.6±10.3 | NS |
| Female, n (%) | 28 (80.0) | 140 (63.3) | 0.01 |
| FBG, (74-106 mg/dL) | 96.3±16.4 | 95.1±12.3 | NS |
| Creatinine,(0.66-1.09 mg/dL) | 0.8±0.1 | 0.9±0.1 | NS |
| ALT, (0-34 U/L) | 22.6±15.6 | 23±14.5 | NS |
| ESR, mm/h | 16±3.2 | 12±2.7 | NS |
| CRP, (0-5 mg/L) | 1.8±0.3 | 1.6±0.5 | NS |
| TSH, (0.4-3.0 IU/mL) | 1.7±1.0 | 1.6±0.9 | NS |
| Homocystein, µmol/L | 13.5 (11-15.9)* | 11.0 (9.5-13.7)* | NS |
| Triglycerides, mg/dL | 133 (91-152)* | 126 (89-160)* | NS |
| HDL-C, mg/dL | 46 (37-59)* | 50 (42-57)* | NS |
| LDL-C, mg/dL | 106 (83.5-126) | 110 (88-136)* | NS |

Abbreviations: FBG: Fasting blood glucose; ALT: Alanine Transaminase; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TSH: Thyroid stimulating hormone; HDL-C:High density lipoprotein; LDL-C: Low density lipoprotein

* Values are presented as median (25-75 interquartile ranges)

p < 0.05 is significant, NS: non-significant

Table 2. The localization of lesions in patients with and without rheumatic disease

| Region | Patient with rheumatic disease (n=35) | Patient without rheumatic disease (n=221) | p |
|--------|-------------------------------------|------------------------------------------|---|
| Periventricular | 15 (39.4%) | 85 (38.5%) | NS |
| Subcortical | 16 (48.5%) | 134 (60.6%) | NS |
| Deep matter | 4 (12.1%) | 2 (0.9%) | 0.003 |

p < 0.05 is significant, NS: non-significant

Table 3. Distribution of patients according to Fazekas scale

| Fazekas scale | Patient with rheumatic disease (n=35) | Patient without rheumatic disease (n=221) | p |
|--------------|-------------------------------------|------------------------------------------|---|
| Grade 1 | 22 (66.7%) | 117 (53.4%) | NS |
| Grade 2 | 9 (27.3%) | 86 (39.3%) | NS |
| Grade 3 | 2 (6.1%) | 16 (7.3%) | NS |

p < 0.05 is significant, NS: non-significant
Similarly, in a migraine study where the Fazekas scale was used, Grade 1 lesions were found to be more frequent in the migraine and control groups. In this study, the lesion burden was similar in the control and patient groups [27]. In another study, patients with sickle cell anemia were investigated for SBI, migraine and headache, but no relationship was detected [28]. In a study involving hypertensive patients, single SBI lesion was detected in 69% of the patients [22]. Our study has many limitations. Two of these are the facts that the study has a limited number of patients and is a cross-sectional retrospective study. Another limitation is that we did not distinguish between rheumatic diseases, which are a heterogeneous group of diseases. Despite these limitations, the exclusion of illnesses that increase SBI risk such as diabetes, hypertension, and chronic renal failure has strengthened the study. Another advantage of our study is that the SBI lesions were evaluated by the same radiologist and the same neurologist. In conclusion, contrary to what we expected, we found that the location and load of SBI lesions were similar in patients with and without rheumatic disease. For this reason, we think that brain MRI findings alone are inadequate in diagnosing SBI without clinical findings and specific laboratory indicators for the patients. The findings of our study should be considered as preliminary and prospective studies involving a larger number of patients should be done.

**Scientific Responsibility Statement**

The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

**Animal and human rights statement**

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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**Conflict of interest**

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.
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