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BRIEF REPORT

Prevalence of abnormal ankle brachial index in patients with primary Sjogren's syndrome

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Abstract Chronic inflammatory autoimmune conditions like rheumatoid arthritis and systemic lupus erythematosus are associated with an increased risk of accelerated atherosclerosis (ATS). Very limited data are available about the incidence of ATS in patients with primary Sjogren's syndrome (PSS). Ankle brachial index (ABI) is a recognized method of detecting subclinical atherosclerosis. The objective of this study was to compare the prevalence of abnormal ABI in patients with PSS and in controls without PSS. Twenty-five PSS patients were compared with an age-, ethnicity-, and sex-matched control group. Traditional risk factors such as smoking, high blood pressure, blood sugar, lipids, and family history of atherosclerosis were assessed in both groups. Baseline clinical and laboratory features of PSS patients were recorded. ABI was measured in both groups. ABI less than 1.0 is considered abnormal. Fifty individuals (25 in each group) were studied. PSS patients and controls did not differ significantly in age, sex, and ethnicity. The prevalence of traditional cardiovascular risk factors was the same in both groups. Five out of 25 PSS patients (20%) had an ABI<1.0 compared to one of 25 (4%) in the control group [P=0.189 (odds ratio (OR)= 6.000 and 95% confidence interval (CI) 0.6464 to 55.692)]. Eight out of 25 PSS patients (32%) had disease duration of more than 10 years. This group of patients had a higher prevalence of low ABI compared to the individuals with lesser disease duration [P=0.02 (OR=16, 95% CI 1.38 to 185)]. PSS patients had a higher prevalence of low ABI, although this did not reach statistical significance. The subgroup of PSS patients with a longer duration of disease had a significantly lower ABI. This study was underpowered and a larger study is required to confirm the findings of this pilot study.

Keywords Ankle Brachial Index · Atherosclerosis · Primary Sjogren's syndrome

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Introduction

Several autoimmune disorders are associated with an increased incidence of premature atherosclerotic disease. In addition to traditional risk factors, non-traditional risk factors such as endothelial activation and excessive vascular remodeling are thought to be behind the progression of atherosclerosis (ATS) in patients with an autoimmune disease. Based on current evidence, ATS may be considered an inflammatory disease characterized by the development of atherosclerotic plaques and ischemic events. Increased prevalence of cardiovascular disease due to premature ATS has been observed in patients with various autoimmune diseases like rheumatoid arthritis [1], systemic lupus erythematosus [2], and Wegener's granulomatosis [3]. As primary Sjogren's syndrome (PSS) is also a chronic autoimmune inflammatory disease, we hypothesized that it may be associated with an increased incidence of atherosclerosis. This study was designed to identify any increased incidence of subclinical atherosclerosis in PSS subjects when compared to controls.

Detecting subclinical atherosclerosis

Various methods of detecting subclinical atherosclerosis have been described. American Heart Association Preventing Conference V has published a review of various non-invasive methods available in detecting subclinical ATS. These include B-mode ultrasound to detect intimal and medial thickness of the large arteries, helical computerized tomography scans to identify calcification of coronary arteries, and magnetic resonance imaging studies of the vessel wall. In addition, endothelial cell function studies, highly sensitive C-reactive protein (CRP) measurements, and measurement of the ankle brachial index (ABI) have also been used.

ABI is considered as a method of predicting cardiovascular disease (CVD) events [4]. The ABI is a relatively cheap and reliable bedside diagnostic test for peripheral arterial disease (PAD) in lower limbs. A systematic review published in 2005 concluded that the specificity of a low ABI to predict future cardiovascular outcomes is high, but its sensitivity is low [5]. Individuals with PAD are more likely to have CVD and cerebrovascular disease than those without PAD. Because of this association, individuals with evidence of PAD should have regular screening and should have aggressive modification of CVD risk factors [6]. Various studies have reported an increased cardiovascular morbidity and mortality in persons with PAD detected by ABI [7–9]. McKenna et al [10] found that when using ABI of less than 0.85 as the criteria, the relative risk for total mortality associated with PAD was 2.36. There was a strong trend for increasing risk with decreasing ABI. They also found that the mortality experience of those with normal ABI was very similar to that of the general US population, whereas the risk for those with an ABI less than 0.4 was markedly elevated in comparison to the US population.

There is no consensus on what constitutes an abnormal ABI. In studies that used ABI as a marker of subclinical atherosclerosis, ABI less than 1.0 was considered abnormal [11, 12] and we also used this as the cutoff value.

Materials and methods

The local ethics committee (Wandsworth Research Ethics Committee) approved the study. Patients who fulfilled the revised version of the European criteria proposed by the American–European Consensus Group for the classification of PSS [13] and with disease duration of more than 5 years were invited to participate. Individuals who matched for age, sex, and race were used as controls. Controls were recruited from the rheumatology clinic and included patients with non-inflammatory problems (osteoarthritis, trochanteric bursitis, epicondylitis). Subjects with a history of diabetes mellitus, ischemic heart disease (defined as a history of myocardial infarction or acute coronary syndrome), cerebrovascular disease (defined as a history of thrombotic cerebrovascular event or transient ischemic attack), peripheral vascular disease (or a history of intermittent claudication), and secondary Sjogren's syndrome were excluded. Written consent was obtained from all the participants.

Data collection Data for age, sex, and ethnicity, clinical features (xerostomia, xerophthalmia), duration of disease, immunological profile (presence of antinuclear antibody (ANA), anti-SSA and anti-SSB antibodies), erythrocyte sedimentation rate (ESR) levels, CRP levels, and biopsy findings were obtained from the medical notes and Electronic Patient Registry of the hospital. Data for family history of atherosclerotic disease were obtained from the case notes and patient interviews. Family history of cardiovascular disease was defined as a myocardial infarction, stroke, or peripheral vascular disease in a first-degree relative. Blood pressure (BP) was measured on the same day of ABI measurement. BP was measured three times on the same visit and the lowest of the three values was recorded. Hypertension was defined as systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg. Fasting blood glucose and lipid profile was obtained by blood sampling on the same day or the next day of the ABI assessment. Hypercholesterolemia is defined as "total cholesterol to high-density lipoprotein cholesterol ratio" of more than 5.

ABI measurement This was measured in accordance with a recent consensus statement on measuring the ABI [4]. The blood pressure cuff is used to measure systolic blood pressure in the brachial artery in both arms by use of an 8-MHz Doppler probe (Huntleigh Health Care *mini* Dopplex®) in the antecubital fossa. The blood pressure cuff is then applied to the ankle, and the Doppler probe is used to determine systolic blood pressure at the left and right posterior tibial arteries and dorsalis pedis arteries. The ABI for each leg is defined as the ratio of the higher of the two systolic pressures (posterior tibial or dorsalis pedis) in the leg and the average of the right and left brachial artery pressures. ABI less than 1.0 in either leg is considered evidence of PAD.

Statistical analysis Two-sample *t* test, Fisher's exact test, and chi-squared test were used to compare variables between groups. In the PSS group, Fisher's exact test was used to test associations between low ABI and other variables. Linear regression analysis (Pearson's correlation coefficient) was used to check for association between age

and disease duration in patients with PSS. *P* value of less than 0.05 was considered statistically significant.

Results

Twenty-seven patients with PSS who satisfied the inclusion criteria were invited to participate. Only two refused and the other 25 were included. Twenty-five controls strictly matched for age, sex, and ethnicity were recruited. The two groups were similar with respect to factors like age, sex, and ethnicity and there was no significant difference in the prevalence of traditional cardiovascular risk factors in both groups but PSS group had high ESR levels compared to the control group (Table 1). The clinical and laboratory features of the patients with primary Sjogren's syndrome are shown in Table 2.

Five patients (10%) with PSS had an ABI of less than 1 in contrast to the control group where only one individual (4%) had an ABI of less than 1. This difference was not statistically significant [*P*=0.1895 (odds ratio (OR)=6.000, 95% confidence interval (CI) 0.6464 to 55.692, Fisher's exact test]. No significant association between decreased ABI and traditional cardiovascular risk factors or presence of anti-SSB antibodies was found (Table 3). As 100% of PSS patients had ANA and anti-SSA antibodies, the relationship between these variables and low ABI was not analyzed. A significant association was noted between decreased ABI and duration of disease. Patients with disease duration of more than 10 years had significantly decreased ABI compared to the individuals with lesser disease duration. [*P* 0.02 (OR 16 and 95% CI 1.38 to 185)]. There was no correlation between age of the patients with PSS and the disease duration when the data were analyzed using linear regression (*P* 0.18). This confirmed that age was not a confounding factor.

Table 1 Demographic features and traditional cardiovascular risk factors of cases and controls

Characteristic	Cases	Controls	*P* value
Age, years (mean, SD)	61.8 (9.1)	63.6 (8.4)	>0.1
Gender (numbers, %)			
Female	24 (96%)	23 (92%)	>0.1
Male	1 (4%)	2 (8%)	
Race (numbers, %)			
Caucasian	10 (40%)	9 (36%)	>0.1
Non-Caucasian	15 (60%)	16 (64%)	
HTN (number, %)	13 (52%)	15 (60%)	>0.1
High TC to HDL ratio (number, %)	2 (8%)	2 (8%)	>0.1
FHx of atherosclerosis (number, %)	7 (28%)	8 (32%)	>0.1
ESR, mm/h (mean, SD)	17.6 (8.9)	8.6 (4.2)	<0.01
CRP, mg/l (mean, SD)	10.5 (8.2)	9.8 (6.8)	>0.1

HTN hypertension, *TC to HDL ratio* total cholesterol to HDL ratio, *FHx* family history, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SD* standard deviation

Table 2 Disease duration and immunology profile of patients with PSS

Disease duration in years, mean (SD)	8.7 (3.2)
Disease duration, number (%)	
Between 5 and 10 years	17 (68%)
More than 10 years	8 (32%)
ANA, number (%)	25 (100%)
Ro (SSA), number (%)	25 (100%)
La (SSB), number (%)	12 (48%)
RF, number (%)	24 (96%)

ANA antinuclear antibody, *RF* rheumatoid factor, *SD* standard deviation

Discussion

There is increasing evidence that chronic inflammation is an independent risk factor for accelerated atherosclerosis. To the best of our knowledge, ours is the first study to look at the prevalence of abnormal ABI in PSS patients. Our results show that patients with PSS have a higher prevalence of abnormal ABI when compared to the normal individuals, although the difference was not statistically significant enough. In addition, we noticed that the subgroup of patients with long-standing disease is more likely to have abnormal ABI than those with a recent diagnosis. This finding is similar to that seen in patients with RA. This identifies a subgroup of patients who should undergo both a careful examination of the entire cardiovascular system and aggressive modification of CVD risk factors. But as this result was obtained from an analysis of a

Table 3 Association between low ABI and other variables in patients with PSS

Characteristics	*P* value
ABI and smoking	NS
ABI and duration of disease of more than 10 years	*P*=0.02
ABI and HTN	OR=16, 95% CI 1.38 to 185
ABI and anti-SSB	NS
ABI and high TC to HDL ratio	NS
ABI and ESR	NS
ABI and CRP	NS
Age and disease duration	*P*=0.186

ABI ankle brachial index, *HTN* hypertension, *TC* total cholesterol, *HDL* high-density lipoprotein, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

small subgroup of the study patients, it should be confirmed by a larger study.

In 2005, Vaudo et al. [14] conducted a case control study with 37 untreated white women with primary SS as cases and 35 age-matched individuals as controls. Carotid and femoral artery intima-media thickness was evaluated and results showed that nearly half of the patients with PSS had subclinical ATS. They also found that this is seen more in PSS patients who had leucopenia and SSA antibodies. In contrast to the study by Vaudo et al., we could not analyze the data for any association between subclinical ATS and SSA antibodies as all of the patients with PSS in our study had SSA antibodies. We did not find any association between low ABI and SSB antibodies. Neither did we find any significant differences in the lipid profile of the two groups. This finding is in contrast to patients with systemic lupus erythematosus, where dyslipidemia has been identified as one of the reasons for increased risk of cardiovascular morbidity.

Our study had many limitations. Firstly, the sample size was small leading to limitation of the usefulness of statistical methods. We feel that a larger study would find statistically significant differences given the fact that 20% of cases had abnormal ABI when compared to only 4% of controls. The second limitation was that all patients were selected from a single department by the principal investigator. This might have led to selection bias. The principal investigator, who was not blinded to the diagnosis, performed the measurement of ABI and this might have led to observer bias.

Disclosures None.

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