Serum Antinuclear Antibodies in Coronary Artery Disease

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Abstract

Background- Inappropriate inflammation is a key mechanism in the development of atherosclerosis. Antibodies against components of the atherosclerotic lesion, in particular, oxidized low density lipoprotein, have been described. The prevalence of systemic autoimmune reactions as characterized by the presence of high titers of serum antinuclear antibodies have also been reported in patients with advanced coronary atherosclerosis. This study was performed to determine whether or not a systemic autoimmune response, characterized by the presence of high titers of antinuclear antibodies, is associated with the presence of coronary atherosclerosis.

Methods- In this case-control study, serum was prepared from 55 subjects (aged 59±9.3) with at least 50% stenoses of three main coronary arteries (3VD subjects), and 41 subjects (aged 52.6±7.6) with no evidence of coronary atherosclerosis (NCA subjects) as determined by coronary angiography. The presence of antinuclear antibodies (ANA) was determined by HEp-2 cell as the substrate using DAKO kits (FITC conjugated rabbit anti-human antibodies) for IgA, IgG, IgM and IgK. The titers of 1/40 or more were considered positive. Observers who graded the test results were unaware of the angiograms.

Results- Ninety-six subjects (mean age 55.8±9.3 years, 40-76 years old) entered the study. Demographic and clinical variables were matched among case and control groups except for age and gender. 3VD groups were older (59±9.3 vs. 52.6±7.6, $p<0.001$) and most of them were male (57.3% vs. 42.7%, $p<0.02$). Among the NCA group, 11 of 41 subjects (27%) were ANA positive and among 3VD patients, 15 of 55 subjects (26.2%) were ANA positive ($p=0.978$).

Conclusion- The presence of ANA, commonly associated with autoimmune diseases, is not substantially more prevalent among subjects with severe coronary atherosclerosis than those with normal coronary arteries. There is no evidence of autoimmune and systemic markers in both groups. This association does not merit further assessment as a potentially useful indicator of increased risk of coronary heart disease ***(Iranian Heart Journal 2006; 7 (1): 11-14).***

Key words: antinuclear antibodies ■ coronary artery disease ■ autoimmune disease

Atherosclerosis is the main cause of coronary heart and cerebrovascular disease, which in turn, are the most common causes of death. It is a multi-factorial process and the importance of inflammation in its pathogenesis has recently been highlighted by different studies.

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A number of inflammatory markers have been reported to be increased in subjects with proven coronary artery disease.

Some studies have shown a rise C-reactive protein is associated with the presence of atherosclerosis.[1]

Autoimmune reactions against heat shock protein 60 can be the initiating event in atherogenesis.[2] Recently a causative role of immunoglobulins in chronic vascular lipid lesion development has been suggested.[3,4]

Some studies have shown that prevalence of serologic markers for CMV in patients with acute coronary syndrome is higher than in patients with stable coronary disease. An elevation in IgG titer for CMV associated with a worse outcome at 30 days and six months.[5]

The prevalence of systemic autoimmune reactions as characterized by the presence of high titers of serum antinuclear antibodies in patients with advanced coronary atherosclerosis has been reported.[6]

In this study we evaluated the association of increased serum titers of antinuclear antibodies with the presence of coronary artery disease.

Methods

Patients

This was a case-control study on fifty-five patients with at least 50% stenoses of three main coronary arteries (3VD subjects) and forty-one subjects with no evidence of coronary atherosclerosis (NCA subjects) determined by coronary angiography.

No subject was diabetic and no one had a history of myocardial infarction in the preceding month. Patients with a history of rheumatologic disease, non-rheumatic valvular heart disease, malignancy, recent viral infection, chronic liver or kidney disease and prolonged febrile illnesses in the preceding months were not included in the study.

They had not taken hydralazine, quinidine or procainamide in the last six months.

Consecutive patients presenting to our cath lab who met the above criteria for either the 3VD group or NCA group were recruited to the study, and they gave informed consent. Before angiography, demographic and clinical data were collected.

An 8-ml blood sample was taken; serum was obtained and stored at –80°C. Then coronary arteriography was performed. Two independent expert cardiologists reported angiography results.

Detection of Immune Markers

The presence of antinuclear antibodies (ANA) was determined by HEp-2 cell as the substrate using DAKO kits (FITC conjugated rabbit anti-human antibodies) for IgA, IgG, IgM and IgK. The titers of 1/40 or more were considered positive. bservers who graded the test results were unaware of the angiograms.

Statistical Analysis

The collected data were analyzed by SPSS 10 software. Differences between case and control groups were assessed with the chi-square test, Fisher's exact test, Mann-Whitney U test (non-normally distributed variables) or Student's t-test. $P<0.05$ was considered significant.

Results

Ninety six subjects (mean age 55.8±9.3 years, 40-76 years old) entered the study. Their demographic and clinical characteristics are shown in Table I. The mean age in the 3VD group was more than the NCA group (59±9.3 vs. 52.6±7.6, $p<0.001$).

Male percentage was more in the 3VD group than NCA subjects (57.3% vs. 42.7%, $p<0.02$). Other baseline variables were matched among case and control groups.

Table I. Patient and control characteristics

	NCA	3VD	P Value
Number	41	55	
Age	52.6±7.6	59±9.3	<0.0001
Male %	42.7	57.3	<0.02
Total cholesterol (mg/dL)	220.6	202.3	0.055
LDL-cholesterol (mg/dL)	143.7	131.9	0.7
HDL-cholesterol (mg/dL)	43.2	43.6	0.94
Triglycerides (mg/dL)	209	187.4	0.17
Systolic BP (mm Hg)	123	122.1	0.73
Diastolic BP (mm Hg)	76.7	76.1	0.74
Current smoker no (%)	10 (24.4)	30 (54.5)	0.004
Ex-smokers no (%)	2 (4.9)	3 (5.5)	1
Previous MI no (%)	0	26 (47.3)	<0.0001

Among the NCA group, 11 of 41 subjects (27%) were ANA positive and among 3VD patients, 15 of 55 subjects (26.2%) were ANA positive (p=0.978).

The incidence of ANA positivity was similar for ex-smokers and current smokers, history of hyperlipidemia, family history and previous Q wave MI as shown in Table II. ANA positivity was not dependent on age; the ANA positive group's age was similar to that of the ANA negative group (54.4±9 vs. 55.5±9.2). Among the 3VD group, 5 out of 18 (27%) had a history of myocardial infarction. The incidence of ANA positivity was not higher among this subgroup than those who had no previous myocardial infarction (11/41, 26.5%). Thus, a documented prior myocardial infarction was not associated with increased incidence of ANA positivity.

Table II. Relation of patient characteristics with ANA positivity

	ANA-positive	ANA-negative	P value
Sex (Male%)	14%	64%	0.032
HLP no (%)	11 (55)	33 (58.9)	0.796
HTN no (%)	8 (40)	25 (44.6)	0.796
Ex-smoker no (%)	1 (5)	2 (3.6)	1
Current smoker no (%)	7 (35)	22 (39.3)	0.794
FH no (%)	2 (10)	1(1.8)	0.168
Previous MI n. (%)	5 (25)	13 (23.2)	1

Discussion

In this study we found that ANA positivity is not higher among coronary artery patients than normal coronary subjects. Our cohorts were not age and sex-matched; the control group was younger and most of them were female.

Brusca et al. studied 139 consecutive patients with myocardial infarction, ischemic stroke or TIA. The control group consisted of 50 sex- matched healthy subjects. ANA at a titer of at least 1/40 were detected in 32% patients with ischemic events and in 26% of healthy subjects. The difference between detection of ANA between the study group and the control group was not significant (p=0.5). The incidence of positive ANA in healthy subjects of this study was similar to our control group's rate (26% vs. 27%), but their case selection was different from ours. It was based on clinical characteristics but our patients were selected by firm angiographic evidence. Also, they included acute ischemic myocardial and cerebrovascular events but our patients were stable and cerebrovascular disease patients were not included.[7]

On the other hand, Grainger et al. have reported association of high titers of serum ANA with the presence of coronary atherosclerosis.

Their case group was also recruited from patients with stable coronary artery disease as was ours.

Their method of ANA detection was also similar to our study. The case and control groups of this study were also not matched for age and sex. Despite these similarities, the results were different.

Furthermore, ANA positivity in normal subjects of their study was lower than ours (17% vs. 27%).[6]

Recently, ANA was also reported as the most frequent autoantibodies detected in 17 (14%) of the 121 patients in patients with early manifestations of peripheral

arterial occlusive disease and a less classical atherosclerotic risk profile.[8]

Conclusion

The presence of ANA, commonly associated with autoimmune diseases, is not substantially more prevalent among subjects with severe coronary atherosclerosis than those with normal coronary arteries.
There is no evidence of autoimmune and systemic markers in both groups. This association does not merit further assessment as a potentially useful indicator of increased risk of coronary heart disease.

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