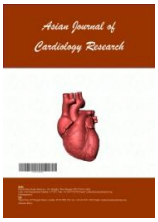

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Antiphospholipid Antibodies in Young Adults with Myocardial Infarction

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Authors' contributions

This work was carried out in collaboration among all authors. Author KT collected the data, managed data compilation and analysis and prepared the manuscript. Meera Sikka designed the study managed data analysis and prepared the manuscript. Author RA managed clinical aspect of the study and helped in patient recruitment. Authors MK, PG and RG managed analysis of laboratory parameters and reviewed the literature. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study aimed to assess the prevalence of antiphospholipid antibodies in young (<45years) patients with MI (myocardial infarction) and to find an association between antiphospholipid antibodies and conventional risk factors of MI.
Study Design: Case control study.
Place and Duration of Study: Departments of Pathology and Medicine, University College of Medical Sciences & Guru Teg Bahadur Hospital, Delhi between November 2018 and March 2020.
Methodology: Forty young MI (<45years) patients and 30 age matched controls were included in the study. Venous blood was collected for Complete blood counts (Automated hematology analyzer), Prothrombin time, Activated partial thromboplastin time (Automated coagulometer), test for Lupus anticoagulant (ISTH criteria), Anticardiolipin antibodies IgG and IgM and Anti-β2-glycoprotein I IgG (ELISA) were done in all patients and controls. SPSS (20) software was used for

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mean, standard deviation, and median values of the quantitative parameters and for all qualitative parameters, their frequencies were obtained. Positivity for antiphospholipid antibodies were expressed in percentages. Association between antiphospholipid antibodies and other risk factors was done using Chi-square test and Fisher's exact test. Odds Ratio was calculated for the various risk factors. *P* less than 0.05 was considered statistically significant.

Results: Conventional risk factors like smoking, obesity, diabetes mellitus, hypertension and dyslipidemia were present in all patients. Antiphospholipid antibodies were detected in 6 (15%) patients and 1 (3.3%) control. Multiple conventional risk factors were present in antiphospholipid antibodies positive patients. No significant association was seen between antiphospholipid antibodies and conventional risk factors of MI.

Conclusion: The study identified antiphospholipid antibodies in 15% young MI patients all of whom also had conventional risk factors. Hence a work-up for these antibodies may be included in these patients.

Keywords: Antiphospholipid antibodies; myocardial infarction; lupus anticoagulant; anticardiolipin antibodies; anti-β2-glycoprotein I.

ABBREVIATIONS

CHD : Coronary Heart Disease
MI : Myocardial Infarction
APLAs : Antiphospholipid Antibodies
APS : Antiphospholipid Syndrome
LA : Lupus Anticoagulant
ACA : Anticardiolipin Antibody
Anti-β2-Gp I : Anti-β2-glycoprotein I
dRVVT : Dilute Russell's Viper Venom Time
BMI : Body Mass Index
HDL : High-Density Lipoprotein
LDL : Low-density lipoprotein

1. INTRODUCTION

Coronary heart disease (CHD) is characterized by an inadequate supply of blood and oxygen to the myocardium [1]. Smoking, raised Apolipoprotein B/Apolipoprotein A1, hypertension, diabetes mellitus, abdominal obesity, psychological factors, poor daily consumption of fruits and vegetables, alcohol consumption, and absence of regular physical activity are known conventional risk factors for CHD [2]. The risk of CHD is 3-4 times higher in Indians, both from urban and rural populations as compared to Americans [3,4]. Myocardial Infarction (MI) is reported to occur at a younger age in Indians with a prevalence of 12-16% [5,6]. About 25% of Acute MIs in India occur in individuals under the age of 40 years and 50% in individuals below the age of 50 years [7]. Thrombophilia or an increased risk of thrombosis is reported to play an important role in the pathogenesis of CHD more so in the young [8].

Antiphospholipid Syndrome (APS) is an autoimmune disease characterized by the presence of antibodies in serum which act against membrane phospholipids. The clinically significant antiphospholipid antibodies (APLAs) include Lupus anticoagulant (LA), Anticardiolipin antibody (ACA) and Anti- β2-glycoprotein I (Anti-β2-Gp I). APLAs induce thrombosis by inhibition of Protein C as also Antithrombin-III, activation of platelets and increased expression of endothelial adhesion molecules. APS can be primary or secondary to other autoimmune diseases [9,10].

Presence of APLAs in a patient with traditional risk factors for CHD further increases the risk of thrombosis and that of MI and is also associated with several adverse consequences [10]. APS was confirmed in 24.6% young patients of Acute MI. Three of these patients underwent a second percutaneous coronary angioplasty due to rapid occlusion of stents. The authors concluded that APS was a concomitant causing disorder of AMI in a quarter of patients and suggested that screening for APLAs should be done routinely in young patients with AMI [11]. Nazir et al conducted a systematic review of studies done on APS patients with Acute MI. These patients were significantly younger (Mean ± SD age 41.1 ± 13.6 years) than typical Acute MI patients (62-68 years). Majority (82%) of patients presented with AMI as the initial presentation. Coronary arteries were normal/with thrombosis in 75% patients. Atherosclerotic narrowing was seen in 25% patients. Recurrence of MI was seen in 6 (16%) patients after 3 months of follow-up. The authors concluded that APS should be considered in young patients with AMI [12]. APS is a largely unrecognized problem in young Indian CHD patients. Conflicting results have been reported on the significance of APLAs in young Indian CHD patients [13,14].

2. MATERIALS AND METHODS

This case control study was set in Departments of Pathology and Medicine, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi. It was carried out on 40 young (<45 years) adults diagnosed with Acute MI using standard criteria [15] and 30 age (±2 years) and sex matched healthy controls. Inclusion criteria required patients to be less than 45 years of age and clinically diagnosed with MI using standard criteria [15]. Patients with a family history of heart disease / any other thrombotic event were excluded from the study.

Venous blood (7.7 ml) was collected from all patients and controls and dispensed as follows for the required investigations: Complete Blood counts (Automated Hematology Analyzer Mindray BC 6800,China), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) (Automated coagulation analyzer Stago, Europe), tests for Antiphospholipid antibodies namely Lupus Anticoagulant (LA sensitive APTT, Dilute Russell's Viper Venom Time (dRVVT) screening and confirmatory), Anticardiolipin Antibody, IgM and IgG (ELISA) and Anti-β2-Glycoprotein I IgG (ELISA) were performed in all patients and controls. In the dRVVT screening test, a screen ratio was calculated which if ≥1.2 suggested the presence of LA. In the dRVVT confirmatory test, a confirm ratio was calculated from which a normalised ratio was derived. A normalised ratio ≥1.2 was confirmatory for LA. Results of biochemical parameters including lipid profile, sugar levels noted from the records. Repeat testing for patients / controls positive for any APLA was done after 12 weeks.

SPSS (20) software was used for Mean, standard deviation, and median values of the quantitative parameters, and for all qualitative parameters their frequencies were obtained. Positivity for APLAs were expressed in percentages. Association between presence of APLAs and other known risk factors was done using Chi-square test and Fisher's exact test. Odds Ratio was calculated for the various risk factors. *P* less than 0.05 was considered statistically significant.

3. RESULTS

Troponin T levels were elevated in all patients. Majority (90%) of patients had ST elevation MI. There was no significant difference in the age of patients (38.8 ± 5.1 years) and controls (37.7 ± 4.9 years). Majority (90%) of patients were between 31-45 years of age, while 86.6% controls were between 31-45 years of age. The study group comprised of 33 (82.5%) males and 7 (17.5%) females. Of the 30 controls, there were 23 (76.7%) males and 7 (23.3%) females.

3.1 Conventional Risk Factors

1. BMI: On the basis of BMI (Body Mass Index), patients were categorised as normal (BMI 18.5-23.0 kg/m^2), overweight (BMI 23-27.5 kg/m^2) and obese (BMI >27.5 kg/m^2) [16,17]. There was no significant (*P*=0.54) difference in the BMI of patients and controls. Five (12.5%), 24 (60%) and 11 (27.5%) patients had a normal BMI, were overweight and obese respectively. BMI was normal in 8 (26.8%) controls, while 11 (36.6%) controls each were overweight and obese.
2. Smoking: A history of smoking was elicited in a significantly (*P*=0.01) higher number of patients (60%) as compared to controls (30%). The years of smoking ranged from 3-20 years in patients and 6-15 years in controls. The number of cigarettes smoked varied between 0.25-2 packs per day in both cases and controls.
3. Hypertension was seen in a significantly (*P*=0.01) higher number of patients (27.5%) as compared to controls (0%).
4. Diabetes Mellitus was seen in a significantly (*P*=0.01) higher number of patients (30%) as compared to controls (0%).
5. Dyslipidemia: One or more lipid parameter was abnormal in 38/40 (95%) patients, the most frequent abnormality being reduced HD (High-Density Lipoprotein) seen in 15 (39.4%) patients followed by reduced HDL together with elevated LDL (low-density lipoprotein) level observed in 5 (13.1%) patients (Table 1).

3.2 Prevalence of Conventional Risk Factors

One or more conventional risk factor was observed in all patients. Seven (17.5%) patients had 1 risk factor while 2 risk factors were observed in 15 (37.5%) patients, 3 risk factors in 14 (35%) patients, 4 risk factors in 3 (7.5%) patients and 5 risk factors in 1 (2.5%) patient.

Table 1. Dyslipidemia in patients and controls

Parameter	Patients (n=40)		Controls (n=30)		*P*
	Number	%	Number	%	
Elevated Cholesterol (>200 mg/dl)	12	30.0	5	16.7	0.19
Elevated Triglycerides (>150 mg/dl)	10	25.0	10	33.3	0.44
Reduced HDL (<40 mg/dl)	31	77.5	23	76.7	0.93
Elevated LDL (>150 mg/dl)	12	30.0	3	10.0	0.07

Table 2. Hematological parameters in patients and controls

	Group		*P*
	Cases (n=40)	Controls (n=30)	
Haemoglobin (g/dl)	12.4±2.1	14.5±1.1	<0.01
RBC($X10^{12}$/L)	4.64±0.76	4.80±0.68	0.36
HCT (%)	38.7±6.7	44.5±3.9	<0.01
MCV (fl)	84.7±11.5	92.8±10.0	<0.01
MCH (pg)	27.1±3.9	30.1±3.1	<0.01
MCHC(g/dl)	31.9±1.3	32.4±1.8	0.14
TLC ($x10^9$/L)	8.4±2.6	7.4±1.9	0.09
Platelet count($x10^9$/L)	235.6±92.9	257.8±80.0	0.17

3.3 Hematological Parameters

Anemia was observed in a significantly (*P*<0.01) higher number of patients (55%) as compared to controls and was mild in majority (54.6%) of patients. MCV and MCH were significantly lower (*P*<0.01) in patients as compared to controls (Table 2).

3.4 Screening Tests of Hemostasis

Prothrombin Time (PT) was significantly (*P*=0.01) higher in patients (Range 11-63 seconds, Mean ± SD 14.8 ± 8.2 seconds) as compared to controls (Range 11-16 seconds, Mean ± SD 12.4±1.7 seconds). PT was prolonged in 9 (22.5%) patients and 6 (20%) controls.

Activated partial thromboplastin time (APTT) was significantly (*P*=0.01) higher in patients (Range 27-86 seconds, Mean ± SD 36.8 ± 14.1 seconds) as compared to controls (Range 18-46 seconds, Mean ± SD 29.7 ± 4.6 seconds). APTT was prolonged in a significantly (*P*<0.01) higher number of patients (16/40, 40%) as compared to controls (3/30, 10%).

3.5 Tests for Antiphospholipid Antibodies

3.5.1 Lupus anticoagulant

LA-APTT and dRVVT screening and confirm test were performed for detection of LA [18]. LA-APTT was significantly (*P*<0.01) higher in patients (41.3±13.4 seconds) as compared to controls (33.6±4.3 seconds). Prolonged LA-APTT (>41 seconds) was observed in a statistically (*P*<0.01) higher number of patients (32.5%) than controls (0%).

3.5.2 dRVVT screening test

dRVVT screen ratio of ≥1.2 was observed in 4 (10%) patients and 1 (3.3%) control.

3.5.3 dRVVT confirmatory test and normalised ratio

A normalised ratio ≥1.2 was observed in 2 (5%) patients confirming the presence of LA, being normal in all controls.

3.5.4 Anticardiolipin antibody IgG

ACA IgG was measured using commercially available kits (ORGENTEC Diagostika GmbH). In patients, the level of ACA IgG ranged from 0.49-9.93 GPL-U/ml with a Mean± SD of 3.00±1.83 GPL-U/ml, the Median being 2.63 GPL-U/ml. In controls, ACA IgG levels ranged from 1.17-6.46 GPL-U/ml, with a Mean± SD of 2.99± 1.39 GPL-U/ml and Median of 2.83 GPL-U/ml. Elevated ACA IgG (10 GPL-U/ml) was not seen in any patient or control.

3.5.5 Anticardiolipin antibody IgM

ACA IgM was measured using commercially available kits (ORGENTEC Diagostika GmbH). In patients, the level of ACA IgM ranged from 0.41-9.99 MPL-U/ml with a Mean± SD of 2.70±2.04 MPL-U/ml and Median of 2.27 MPL-U/ml. In

controls, the level of ACA IgM ranged from 0.22-4.11 MPL-U/ml, with a Mean± SD was 1.75±0.92 MPLU/ml and Median of 1.63 MPL-U/ml. Elevated ACA IgM (7 MPL-U/ml) was seen in 2 (5%) patients and none of the controls (*P*=0.50).

3.5.6 Anti-Beta2-glycoprotein I

Anti-β2-GpI was measured by ELISA using commercially available kits (ORGENTEC Diagostika GmbH) in all patients and controls. In patients, Anti-β2-GpI levels ranged from 1.06-10.81 U/ml with a Mean± SD of 2.25±1.66 U/ml and Median of 1.64 U/ml. In controls, Anti-β2-GpI levels ranged from 0.79-36.62 U/ml with a Mean± SD of 2.75±6.44 U/ml and Median of 1.35 U/ml. Elevated levels (>8 U/ml) levels were seen in 2(5%) patients and 1 (3.3%) control(*P*=0.99).

Repeat testing was done in patients and controls positive for any APLA after 12 weeks. A persistent positive result was observed in all patients and controls. Thus, one or more APLAs were present in 6 (15%) patients and 1 (3.3%) control (Table 3).

3.5.7 Association of APLAs and conventional risk factors

APLA positivity was higher in smokers (20.8%) as compared to non-smokers (6.2%) (*P*=0.37). APLA positivity was were higher in non-diabetics (21.4%) as compared to diabetics (0%), (*P*=0.15). APLA positivity was higher in normotensive patients (17.2%) as compared to hypertensive patients (9.1%), (*P*=0.99). Of patients with normal BMI, overweight and obesity, APLA positivity was seen in 1 (20%), 3 (12.5%) and 2 (18.2%) patients respectively (*P*=0.85).

The number of APLA positives were higher in patients who had increased cholesterol levels (25%) as compared to patients who had normal cholesterol levels (10.7%) (*P*=0.34).Similar observations were made in patients with increased triglyceride levels (*P*=0.62),reduced HDL levels(*P*=0.71) and elevated LDL levels (*P*=0.05).No significant association was seen between APLAs and conventional risk factors (Table 4).

3.5.8 Conventional risk factors in APLA positive patients

Multiple risk factors of MI were present in APLA positive patients. Five (83.3%) patients were smokers, 1 (16.6%) patient had hypertension, 2 (33.3%) patients were obese and 6 (100%) patients had dyslipidemia. None of the patients had diabetes mellitus.

4. DISCUSSION

CHD is the most common, serious chronic illness [1]. Traditional risk factors such as diet, lack of physical activity, abnormal lipids, diabetes, and hypertension account for most of the risk for MI worldwide [1]. In developed countries, health initiatives against these major risk factors has led to a 2-3% annual decline in the prevalence of CHD [19]. However, the estimated number of CHD patients in India has increased considerably in both rural and urban populations [4]. In India, the disease occurs at a younger age with several adverse consequences including high mortality [19]. Many of these patients lack conventional risk factors. Thrombophilia is reported to play an important role in the pathogenesis of CHD [8]. APS is an acquired prothrombotic state characterized by the presence of APLAs which presents clinically as arterial or venous thrombosis. MI has been reported in patients of APS [10]. This study evaluated APLAs in young patients with MI.

One or more conventional risk factors was observed in all patients. A high number of patients and controls were overweight and obese. Twenty-four (60%) patients and 11 (27.5%) patients were overweight and obese respectively. Whereas, 11 (36.6%) controls each were overweight and obese respectively.

A history of smoking was elicited in a significantly (*P*=0.01) higher number of patients (60%) as compared to controls (30%) and was limited to males.

This study observed hypertension in a significantly (*P*<0.01) higher number of patients (27.5%) as compared to controls (0.0%). Diabetes Mellitus too was observed in a significantly (*P*<0.01) higher number of patients (30%) as compared to controls (0%).

Dyslipidemia was frequent in this study, one or more lipid parameter being abnormal in 38/40 (95%) patients.

4.1 Tests for Antiphospholipid Antibodies

Lupus Anticoagulant (LA) is a heterogeneous circulating autoantibody directed against

epitopes on negatively charged phospholipid binding proteins which prolongs phospholipid-dependent coagulation reactions in vitro. Clinically, LA has been implicated in arterial and venous thrombosis [20]. In this study, LA was identified in 2 (5%) patients. In a study on 40 young patients with MI, LA was detected in 6 (15%) patients [13]. However, Singh et al did not detect LA in any of 24 young patients with MI [14].

Elevated level of ACA IgG (10 GPL-U/ml) was not seen in any patient or control. Elevated level of ACA IgM (7 MPL-U/ml) was seen in 2 (5%) patients and none of the controls(*P*=0.50). Similar results were reported in a study on 307 patients with AMI and 160 patients with unstable angina. IgG ACA was not significantly increased in any patient as compared to controls. Only 2 patients had a high positive IgM, one on admission and one at 12 months [21]. Singh et al reported elevated levels of ACA IgG and IgM in 4.16% young patients with MI as seen in the present study [14]. In contrast, a study on young Indian male patients with MI and controls observed elevated ACA levels in 9 (22.5%) patients and 2(4%) controls. The raised isotype was IgG in all patients except one in whom there was a concomitant elevation of IgM [13].

Table 3. Prevalence of APLAs in patients and controls

APLA	Patients (n=40)		Controls (n=30)	
	No.	%	No.	%
LA	2	5	0	0
ACA IgG	0	0	0	0
ACA IgM	2	5	0	0
Anti-β2-Gp I	2	5	1	3.3
Total	6	15	1	3.3

LA-Lupus anticoagulant, ACA-Anticardiolipin antibody, Anti-β2-Gp I- Anti- β2-glycoprotein I

Table 4. Association of APLAs with conventional risk factors

	APLA +ve		APLA -ve		Odds Ratio	p Value
	Number	%	Number	%		
Smoking status						
Smoker	1	6.2	15	93.8	3.94	0.37
Non-Smoker	5	20.8	19	79.2		
Diabetes Mellitus						
Absent	6	21.4	22	78.6		0.15
Present	0	0.0	12	100.0		
Hypertension						
Absent	5	17.2	24	82.8	2.08	0.99
Present	1	9.1	10	90.9		
BMI						
Normal	1	20.0	4	80.0		0.85
Overweight	3	12.5	21	87.5	1.75	
Obese	2	18.2	9	87.8	1.12	
Total Cholesterol						
Normal	3	10.7	25	89.3	2.78	0.34
Increased	3	25.0	9	75.0		
Triglyceride						
Normal	4	13.3	26	86.7	1.62	0.62
Increased	2	20.0	8	80.0		
HDL						
Normal	1	11.1	8	88.9	0.65	0.71
Decreased	5	16.1	26	83.9		
LDL						
Normal	2	7.1	26	92.9	6.5	0.05
Increased	4	33.3	8	66.7		

Elevated (>8 U/ml) levels of Anti-β2-Gp I were seen in 2 (5%) patients and 1 (3.3%) control(*P*=0.99). A study on 1712 randomly selected patients to assess the prevalence of APLAs and their association with subclinical atherosclerosis using carotid artery intima media thickness, identified Anti-β2-GpI in 4.3% patients with 1.2% at high titer and a significantly (*P*<0.001) higher prevalence in older patients [22].

According to Modified Sapporo criteria, a diagnosis of APS is considered if there is clinical evidence of at least one thrombotic event in the presence of a positive laboratory test for APLA which is confirmed 12 weeks after the initial positive result [23].

In this study, APLAs- LA, ACA (IgM and IgG) and Anti-β2-Gp I (IgG) were present in 6 (15%) patients and 1 (3.3%) control and were positive even after 12 weeks of initial testing. Multiple conventional risk factors were present in APLA positive patients. Five (83.3%) patients were smokers, 1 (16.6%) patient was hypertensive, 2 (33.3%) patients were obese and all 6 (100%) patients had dyslipidemia. None of the patients had diabetes mellitus.

In this study, there was presence of one or more conventional risk factors in patients with myocardial infarction including those with positive APLAs. However, no significant association was seen between APLAs and conventional risk factors. Adler et al also did not observe an association between APLAs and any conventional cardiovascular risk factor. They concluded that APLAs are an independent risk factor for AMI and may play a role in its development [24].

5. CONCLUSION

While it has been observed in some studies that screening for APS should be done in young MI patients with no conventional risk factors, this study detected APLAs in 6 (15%) young patients with MI in whom conventional risk factors were seen in all patients. Co-existence of APS with traditional risk factors further increases the risk of developing thrombosis which tends to be recurrent. Many patients with APS are asymptomatic. Considering the prevalence of APLAs in young MI patients, as observed in this study, along with conventional risk factors, it is suggested that a work-up for APS may be included in young patients with MI. Studies on a larger number of patients are required to further corroborate these findings.

DISCLAIMER

The products for this research are commonly and predominantly use products in our areas of research and country. There is absolutely no conflict of interests between the authors and producers because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

CONSENT

A written informed consent was obtained from all patients and controls.

ETHICAL APPROVAL

The study received clearance from the Institutional Ethics Committee for Human Research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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