



STUDY ON TAKAYASU ARTERITIS FROM NORTH EASTERN INDIA: PRESENTATION AND CARDIOVASCULAR MANIFESTATIONS

Cardiology

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ABSTRACT

Background: The cardiac manifestations in TA are the consequences of the various features related to TA; hypertension, pathologic involvements of the pulmonary/coronary artery, aortic regurgitation as well as direct involvement of the myocardium. Cardiac manifestations may represent another type of cardiovascular morbidity in TA patients.

RESULTS: Among the 112 TA patients, 80 patients (71.42%) were female. The female to male ratio was 2.5: 1. Most of the patients experienced clinical signs or symptoms attributable to the disease at the age of less than 40 years. The mean age of the patients was 26.83 ± 9.94 years. Hypertension was the most common coexisting disease 72%. Diabetes mellitus, dyslipidemia were found in 4% and 36/112 (32.14%) patients, respectively. Those co-morbidities including hypertension, diabetes mellitus, and cerebrovascular events, etc. showed no statistical difference between the active and inactive TA groups. The common presenting symptoms were those that suggested vascular insufficiency; claudication (33%), fever (5%), lethargy (4%), arthralgia (3%) and carotidynia in some of the patients. 60 (53.57%) were classified as the active group at the time of the initial diagnosis. Out of the 80 females, 40 were in the active group and remaining 40 were having inactive disease. Incidence of bruit was slightly higher in patients with active disease than inactive disease. However, overall there was no statistical difference in the clinical symptoms and signs between the two groups. Most common symptom that suggested acute inflammation was fever and was found mainly in active takayasu arteritis group. The left subclavian artery was the most frequently involved branch followed by left common carotid artery, descending aorta and right common carotid artery. Generally, the most frequent feature of the involved vessels was stenosis except for the ascending thoracic aorta. The ascending thoracic aorta frequently appeared to have dilatation or aneurysmal change. Pulmonary artery involvement were observed in 3.57% patients. When these involved vessels were categorized by the International TA Conference in Tokyo 1994 classification, TYPE I (21.42%), TYPE IIA (14.28%), TYPE IIB (3.57%), TYPE III (10.71%), TYPE IV (3.57%), TYPE V (46.42%). TYPE V was the most common type followed by TYPE I, TYPE IIA and TYPE III. The active TA patients had more frequent involvement of the ascending aorta, aortic arch and its main branches (right innominate artery, both common carotid arteries, both subclavian arteries) than did the inactive group. Among 112 patients, 10.71% (12/112) patients underwent coronary angiography following symptoms suggestive of myocardial ischemia. CAG showed evidence of coronary artery disease with involvement of left anterior descending in the form of ostial lesion in 4 patients and 8 of them having double vessel disease.

CONCLUSION: TYPE V was the most common type followed by TYPE I, TYPE IIA and TYPE III. The active Takayasu Arteritis patients had more frequent involvement of the ascending aorta, aortic arch and its main branches than did the inactive group. The left subclavian artery was the most frequently involved branch followed by left common carotid artery, descending aorta and right common carotid artery. Hypertension was the most common coexisting disease.

KEYWORDS

Takayasu arteritis, Cardiovascular Manifestations, CT Angiography, Echocardiography

INTRODUCTION

Takayasu arteritis (TA) is systemic inflammatory disease involving the aorta and its main branches. The initial prominent finding of TA is granulomatous inflammation in the adventitia and medial wall of the involved vessels. It progresses to fibrosis and causes stenosis or occlusion in the lesions. In the advanced stage, destruction of the elastic fibers in the medial wall can cause dilatation or aneurysmal changes.[1] The progression of vascular lesions is known to be related to the disease activity of TA. In patients with active progressive disease, the established vascular abnormalities further advance to stenosis or dilatation. The outcome of intervention or bypass surgery for the involved vessels is influenced by the TA activity.[2] Cardiac manifestations may represent another type of cardiovascular morbidity in TA patients. The cardiac manifestations in TA are the consequences of the various features related to TA; hypertension, pathologic involvements of the pulmonary/coronary artery, aortic regurgitation as well as direct involvement of the myocardium.[3] However, the cardiovascular manifestations and their relationship with disease activity have not been evaluated in a systemic manner especially in India. In this background, this study was undertaken to evaluate the pattern of cardiovascular involvement in patients with TA and to assess whether disease activity of TA affects the cardiovascular manifestations by studying the specified disease profiles, the angiographic findings and the echocardiographic measurements.

MATERIALS AND METHODS :

The Hospital based prospective observational study was carried out in

Department of Cardiology of a tertiary health care centre in North East India over a period of 1 year. Convenient sampling method was done to include all consecutive samples. Informed consent was taken from all patients satisfying the inclusion and exclusion criteria given. Inclusion criteria comprised all patients with the diagnosis of TA according to the 1990 American College of Rheumatology criteria which is as follows: At least three of the following need to be satisfied: Age at disease onset ≤ 40 years, Claudication of the extremities, Decreased brachial artery pressure, A blood pressure difference between both arms ≥ 10 mmHg, Bruit over the subclavian arteries or aorta, Abnormalities on arteriography. Exclusion criteria comprised renal failure precluding arteriography, not willing to participate

METHODOLOGY:

Patient records included the clinical history of TA (signs and symptoms at onset and the time of the first diagnosis), the co-morbid diseases and the laboratory, angiographic and echocardiographic findings at the time of the initial diagnosis. Co-morbid diseases included hypertension, diabetes mellitus, dyslipidaemia, congestive heart failure. The vascular lesions will be evaluated with various imaging modalities including CT angiography (MR angiography and duplex ultrasonography only if indicated). Echocardiographic examinations, involving 2D, M-mode and Doppler techniques were performed. The active group with disease activity satisfied one of the criteria of i) an elevated ESR (>20 mm/h) or CRP level ii) a thickened arterial wall (>3 mm) with mural enhancement on either CT angiography or T1-

weighted high-resolution spin-echo MRI and iii) carotid tenderness (carotidynia) at the time of the initial diagnosis. Patients who attended Department of Cardiology between February 2017 and January 2018 were identified. All of them satisfied the 1990 American College of Rheumatology criteria, which fulfills at least 3 of the following: an age at disease onset ≤ 40 years, claudication of the extremities, a decreased brachial artery pressure, a blood pressure difference between both arms ≥ 10 mmHg, bruit over the subclavian arteries or aorta, and abnormalities on arteriography.

CLINICAL EXAMINATION AND CT ANGIOGRAPHY:

Retrospectively and prospectively medical records of the patients were reviewed. The records included the clinical history of TA (signs and symptoms at onset and the time of the first diagnosis), the co-morbid diseases and the laboratory, angiographic and echocardiographic findings at the time of the initial presentation. Co-morbid diseases were defined as follows: hypertension as blood pressure persistently higher than 140/ 90 mmHg or currently taking antihypertensive medication, diabetes mellitus as HbA1c level of $\geq 6.5\%$ or more, dyslipidemia as a total cholesterol level over 200 mg/dl, a LDL level over 130 mg/dl, azotemia as a creatinine level over 2.0 mg/dl and congestive heart failure as pulmonary edema or pleural effusion seen on a chest radiography or rales heard on a physical examination. Most of the patients' initial CBC, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) level and creatinine level were identified. The vascular lesions were evaluated with various imaging modality mainly CT angiography and duplex ultrasonography. Among 112 patients, all patients underwent CT angiographic evaluation. The evaluation of the coronary artery was performed in 12 selected patients with chest pain suspicious of a cardiac origin or there was evidence of cardiac ischemia. The angiographic types were classified using the International TA Conference in Tokyo 1994 angiographic classification. Echocardiographic examinations, involving 2D, M-mode and Doppler techniques, were performed in 112 patients at the time of initial diagnosis. The echocardiographic measurements were made according to the guideline of the American Society of Echocardiography. Valvular regurgitation of more than a mild degree was considered significant, and this was used in the analysis. The pulmonary artery systolic pressure (PASP) was measured in patients who showed a traceable jet of tricuspid regurgitation (TR). The patients having a TR peak gradient over 30 mmHg were defined as having pulmonary hypertension. The severity of pulmonary hypertension was classified according to the values of PASP; a PASP of >40 mmHg was mild, a PASP of 50–70 mmHg was moderate and a PASP over 70 mmHg was severe pulmonary hypertension. Doppler study of both carotid arteries were carried out in all 112 patients. The active group with disease activity was categorized as satisfying one of the criteria of i) an elevated ESR (>20 mm/h) or CRP (>0.9 mg/dl) level, ii) a thickened arterial wall (>3 mm) with mural enhancement on either CT angiography and iii) carotid tenderness (carotidynia) at the time of the initial diagnosis. The approval of the local institutional review board was obtained, and informed consent was taken.

STATISTICAL ANALYSIS:

Descriptive statistics were expressed as mean \pm standard deviation (SD) for continuous variables and proportion (%) or frequency for categorical variables. Differences between the groups with high disease activity and low disease activity has been examined by univariate analysis. P values less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software package (SPSS for Windows, version 22.0; SPSS, Inc., Chicago, IL, USA).

BASELINE CHARACTERISTICS:

	MEAN	STANDARD DEVIATION (SD)	RANGE
AGE (in years)	26.83	± 9.94	(7-45)
ESR (mm/hr)	35.35	± 21.08	(10-70)
CRP	16.59	± 17.07	(.2-45)
EF(%)	53.39	± 7.63	(40-60)
HDL (mg/dl)	37.46	± 7.82	(22-54)
LDL (mg/dl)	118.42	± 33.52	(78-200)
TRIGLYCERIDE (mg/dl)	147.57	± 45.28	(80-260)
CIMT in mm	1.57	$\pm .49$	(1-2)
TLC /cumm	9957.67	± 3984.42	(4700-16000)

RESULTS AND ANALYSIS:

Among the 112 TA patients, 80 patients (71.42%) were female. The female to male ratio was 2.5: 1. Most of the patients experienced clinical signs or symptoms attributable to the disease at the age of less than 40 years. The mean age of the patients was 26.83 ± 9.94 years. Hypertension was the most common coexisting disease 72%. Diabetes mellitus, dyslipidemia were found in 4% and 36/112 (32.14%) patients, respectively. Those co-morbidities including hypertension diabetes mellitus, and cerebrovascular events, etc. showed no statistical difference between the active and inactive TA groups. The common presenting symptoms were those that suggested vascular insufficiency; claudication (33%), fever (5%), lethargy (4%), arthralgia (3%) and carotidynia in some of the patients. 60 (53.57%) were classified as the active group at the time of the initial diagnosis. Out of the 80 females, 40 were in the active group and remaining 40 were having inactive disease. Incidence of bruit was slightly higher in patients with active disease than inactive disease. However, overall there was no statistical difference in the clinical symptoms and signs between the two groups. There was no statistically significant difference in the prevalence of signs like claudication, dizziness or headache, weak pulses of extremities. Most common symptom that suggested acute inflammation was fever and was found mainly in active takayasu arteritis group.

LABORATORY FINDINGS:

Among the patients, 50 % had anemia. Elevated ESR (>20 mm/h) and CRP (>0.9 mg/dl) levels were found in 53.57% (60/ 112) and 48.21 % (54/112) of the patients. When the laboratory data was compared according to the disease activity, the active TA group showed a higher WBC count, and a lower hemoglobin level (12.9 ± 1.7 vs 12.0 ± 1.7 g/dl, respectively) with a statistically significant difference ($p < 0.001$). This suggested systemic inflammation and anemia of a chronic disease in the active TA group. Anemia was more prevalent in the active group ($P < 0.057$).

ANGIOGRAPHIC FINDINGS:

The involved segments of the aorta were as follows: Ascending aorta 28/112, arch of aorta 42.85% (48/112), descending aorta 57.14% (64/112), innominate artery (39.28%) 44/112, right common carotid artery (42.85%) 48/112, left common carotid artery (58.92%) 66 /112, right subclavian artery (41.07%) 46/112, left subclavian artery (71.42%) 80/112, left internal carotid artery (14.28%) 16/112, right internal carotid artery 10.71% (12/112), left renal artery 32.14% (36/112), right renal artery 32.14% (36/112), pulmonary artery 3.57% (4/112), superior mesenteric artery 12.5% (14/112), celiac artery 21.42% (24/112), vertebral artery 14.28% (16/112), internal iliac artery 3.57% (4/112), external iliac artery 3.57% (4/112). The left subclavian artery was the most frequently involved branch followed by left common carotid artery, descending aorta and right common carotid artery. Generally, the most frequent feature of the involved vessels was stenosis except for the ascending thoracic aorta. The ascending thoracic aorta frequently appeared to have dilatation or aneurysmal change. Pulmonary artery involvement were observed in 3.57% patients. Among 112 patients, 10.71% (12/112) patients underwent coronary angiography following symptoms suggestive of myocardial ischemia. CAG showed evidence of coronary artery disease with involvement of left anterior descending in the form of ostial lesion in 4 patients and 8 of them having double vessel disease.

CAROTID INTIMAL MEDIAL THICKNESS:

Doppler study of common carotid arteries were carried out in all patients. The examiner was blinded regarding the disease activity of the patient. Carotid intimal medial thickness (CIMT) which is considered an early marker of atherosclerosis was measured on both common carotid artery. Common carotid intima media thickness CIMT) and presence of carotid plaques are known to be risk factors for the development of vascular events and to be independent from the conventional risk factors. CIMT was considered pathological if the value was found to be >0.9 mm and also if B mode ultrasound showed plaque in common carotid artery with any evidence of stenosis. 42.85% (48/112) patients had CIMT >0.9 mm showing early evidence of atherosclerosis.

ECHOCARDIOGRAPHY:

Among the 112 patients who underwent echocardiographic evaluation, they showed relatively normal LV systolic function LVEF 60%. 102 patients had LVEF of 60%, 6 patients had mild LV dysfunction, 4 patients had moderate LV dysfunction which improved

to normal LV function once the disease activity was controlled. 18 patients had mild mitral regurgitation (MR), 6 patients had moderate MR. 22 patients had mild aortic regurgitation. Pulmonary hypertension was observed in 28 patients among the 112 patients. 22 patients had mild pulmonary hypertension, 6 patients had moderate pulmonary hypertension. LVEDD and LVESD between the patients with active and inactive disease were not statistically significant. There was statistically significant difference in ejection fraction between active and inactive group.

DISCUSSION:

The purpose of the study was to see the cardiovascular manifestations of Takayasu arteritis. This is an observational study from a tertiary centre in North Eastern India. Corroborating the literature, prevalence of takayasu arteritis is found to be more in females affecting younger age groups in our study. Thirty patients were in the active group. Patients having active disease were found to be having more widespread involvement of blood vessels. In our study, 53.57% of the TA patients were classified as having active TA. The previous studies reported that the proportion of active disease ranged from 32% to 84.3% . [4][5] Ga Yeon Lee et al in their study comprising 204 takayasu arteritis patient showed the number of patients with active disease at presentation to be 69.3%.[6] However, it is important to highlight that the definition of active disease in TA is not standardized. There is no consensus guidelines. Assessment of activity of disease in TA is always challenging as the clinical, biological, radiological and other imaging data do not always correlate.[7] There is no validated tool worldwide to measure activity of disease. As in other inflammatory disorders, search for a convenient, reliable, and validated biomarker for Takayasu arteritis still continues. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels is frequently advocated for disease assessment in TAK, despite being shown to be neither sensitive nor specific enough to monitor disease activity.[8] Active disease can be present in 23% of patients with TAK who shows normal laboratory parameters. Also, ESR can be elevated in only 72% of patients considered to have an active disease and was still high in of patients considered to be clinically inactive. Serum autoantibodies such as anti-endothelial antibodies [9] and serum biomarkers such as IL-6, IL-8, IL-18, and matrix metalloproteinase-9 have been suggested as candidate biomarkers of disease activity. Conventional digital subtraction angiography is the —gold standard for detecting stenosis, occlusions, and aneurysms that characterize the latter stages of TAK; however, it is the least sensitive method for visualizing wall thickness. Ultrasonography has recently been extensively studied in TAK, particularly to investigate the changes in carotid arteries. Doppler US can detect stenosis in carotid arteries with high sensitivity (90%) and specificity (91%).[10] A scoring system for TAK assessment with color Doppler US (CDUS.K) has also been recently presented.[11] This score examines 19 vascular regions in a standardized manner, scoring each for both stenosis and flow pattern. The correlation with the angiography score was good; however, intrathoracic vessels, such as the commonly involved subclavian arteries, were particularly difficult to visualize and produced the lowest kappa values in this study. Contrast-enhanced MRA or CT angiography (CTA) allows non-invasive imaging of the aorta and its major branches. Although MRA appears to be highly accurate, sensitive, and safe compared with invasive angiography in the diagnosis of TAK, [12] 2% of stenotic arteries were wrongly portrayed as occluded in a previous study. The complexity of evaluating disease activity in TA is further underlined by the fact that up to 45% of the patients in clinical remission have histological evidence of active disease.[13] The global activity criteria, such as National Institute of Health (NIH) criteria, must be taken under consideration with caution given the lack of validated activity criteria [15] Also, NIH criteria and DEI-TAK criteria [15] need information regarding new onset or worsening of clinical features such as vascular ischemia and angiographic features during patient's follow-up. Mural changes in CT or MRI have been shown to predict disease activity and response to immunosuppressive therapy. Mural changes indicative of an active TA lesion in CT angiography are a thickened arterial wall with mural enhancement and a poorly attenuated ring on delayed phase images.[16] On evaluating serially, CT evaluation for the patients with active TA showed a decrease of the mural thickness and enhancement during follow-up period.[17] When these involved blood vessels were categorized by the International TA Conference in Tokyo 1994 classification, TYPE I (24, 21.42%), TYPE IIA (16, 14.28%), TYPE IIB (4, 3.57%). TYPE III (12,10.71%), TYPE IV (4, 3.57%), TYPE V(52, 46.42%). TYPE V was the most common type followed by TYPE I, TYPE IIA and TYPE III. In contrast to the previous findings from study in India where TYPE IV and TYPE III were found to be more common [18], in our study Type V was most common followed by TYPE I, TYPE IIA and TYPE III. Japan, North America, Mexico and China are known to have TYPE V, TYPE II and TYPE I as the most

common variants in sequence.[19][20] The active TA group had more extensive types (types V, II) involving multiple vessels, including the aortic arch branches, than the inactive TA group. 19.64% patients had mild aortic regurgitation. AR has been reported to occur in 7 to 16% of TA patients.[21] Ga Yeon Lee et al in their series found 18% of the patients having AR and was seen more frequently in patients with active Takayasu Arteritis group.[22] It may be postulated that direct inflammation of the aortic leaflets rather than a dilatation of the aortic root is the main mechanism of developing AR in active TA. Pulmonary hypertension was observed in 28 (25%) patients among the 112 patients. 22 (19.64%) patients had mild pulmonary hypertension, 6 (5.35%) patients had moderate pulmonary hypertension. Pulmonary hypertension in Takayasu arteritis could be caused either by direct involvement of the pulmonary artery or by the elevated LV filling pressure, which leads to backward pressure on the pulmonary artery. In case of TA, LV filling pressure can be elevated by hypertension, LV hypertrophy, LV systolic dysfunction, LV diastolic dysfunction and also aortic regurgitation. The LV wall thickness and EF showed no statistical difference between the groups. No significant difference in hypertension was found between both groups. Acute phase reactants like ESR and CRP were elevated in patients with active disease. Patients with active disease had higher incidence of left ventricular systolic dysfunction, pulmonary hypertension, AR and MR. However the study has its own limitations. Firstly, this is an observational study. So it is difficult to draw a conclusion from the study. Data collected is single centre based. The total number of patients is less, so general representation of the disease under study is not possible. Also patients have been evaluated mainly during presentation. Proper follow up has not been done. Initial features of TA could be easily disturbed during the time of individualized management.

CONCLUSION

Patients with active disease had higher incidence of left ventricular systolic dysfunction, pulmonary hypertension, AR and MR. TYPE V was the most common type followed by TYPE I, TYPE IIA and TYPE III. In contrast to the previous findings from study in India where TYPE IV and TYPE III were found to be more common, in our study Type V was most common followed by TYPE I, TYPE IIA and TYPE III.

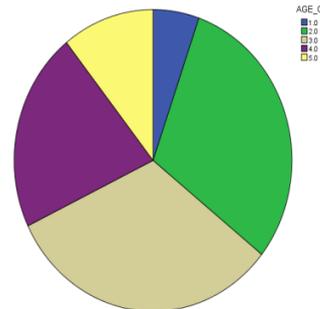


Figure 1 showing age distribution (groupwise). Blue segment (number 1) representing age group from 0-10 years of age, green (number 2) from 11-20 years of age, brown (number 3) from 21-30 years of age, purple (number 4) 31-40 years of age, yellow (number 5) 51-60 years of age



Figure 2 is a coronal section of the arch of aorta (Contrast enhanced CT scan of aorta and its branches) showing severe wall thickening with enhancement and near total occlusion of Left Common Carotid Artery (LCCA) starting at its origin



Figure 3 is (CT scan of abdominal aorta) axial sections at level of superior mesenteric artery (SMA) showing SMA and Abdominal aortal wall thickening.

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