

Ten-year Investigation of Clinical, Laboratory and Radiologic Manifestations and Complications in Patients with Takayasu's Arteritis in Three University Hospitals

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Abstract

Background: Takayasu arteritis is a condition of unknown aetiology that affects the aorta and its primary branches. The disease has been primarily recognised and described in Asia. The aims of this study were to identify the main clinical, laboratory, and angiographic features of Takayasu arteritis in Iranian patients over a 10 year period from 2000 to 2010.

Methods: Data were obtained from angiographic and medical records of patients treated at Shahid-Rajai, Taleghani, and Loghman Hospitals during the above-mentioned time period. The criteria for definitions and findings were those proposed by the American College of Rheumatology.

Results: A total of 15 patients were identified. The median age at presentation was 36 years and 73.3% of patients were females. Fever was the most common presentation. According to "modified" National Institute of Health criteria, 44.7% of patients were in the acute phase of disease with systemic symptoms such as fever, weight loss, and elevated C-reactive protein (CRP) levels. Immunological markers such as antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (C-ANCA) were absent. The tuberculin test result was positive in 40% of the patients. Vascular bruit was present in 86.7% and hypertension was detected in 53.3% with 13.3% having associated renal artery stenosis. The angiographic manifestations were classified as; type I, cervicobrachial type (26.6%); type II, thoracoabdominal type (20.0%); type III, peripheral type (6.6%); and type IV, generalised type (46.7%). Coronary arteries were involved in three cases, pulmonary in two and renal in two.

Conclusion: Based on our findings, the most common clinical, laboratory and angiographic findings were fever, increased erythrocyte sedimentation rate (ESR) and stenosis, respectively. Because of dangerous consequences of this disease, attention to fever and increased ESR, especially in young women may be helpful for physicians to prevent diagnosis delay.

Keywords: Takayasu arteritis, systemic vasculitis, arteriography, claudication, tuberculosis

Introduction

Takayasu's arteritis (TA) is a chronic inflammatory disease of unknown aetiology. The mechanism of this disease is not exactly defined. The inflammatory process is generally (but not exclusively) initiated in the second or third decade of life through the actions of non-specific inflammatory cells. As the disease progresses, fibrotic stenosis occurs in aorta and its main branches (1–3). The consequence of this inflammatory process can be stenosis, thrombosis, dilatation or aneurysm formation in aorta and/or its branches (4).

Majority of cases have been observed in Asia, Africa, and Latin America (5). In Asia, its incidence (2.6 in a million per year) has been reported to be 100 times higher than in Europe and North

America (6). Because of the delay in diagnosing the disease, patients often experience claudication, absence of pulses, hypertension, myocardial infarction (MI), and cerebrovascular accidents (CVAs) (7). Accurate and early diagnosis of TA can reduce the economic, social, and psychological burdens. Considering the fact that classical TA has mainly been described in Asia, precise assessment of its clinical and radiologic presentations and determination of its main pattern of presentation in our region can potentially be useful for early diagnosis, thereby preventing complications and improving the quality of life for the patients. At present, there is a paucity of studies investigating dilatation and aneurysm in TA in our region. The aims of the study were to identify the main

clinical, laboratory, and angiographic features of Takayasu arteritis in Iranian patients from three hospitals in Tehran over a 10 year period from 2000 to 2010.

Materials and Methods

This cross-sectional study included 15 TA patients and was conducted over a 10-year period from 2000 to 2010 in three university hospitals in Tehran. If patients died during the study, it was noted in questionnaire designed for this purpose; death associated with TA was also recorded. The inclusion criteria were the existence of at least three of the American College of Rheumatology (ACR) criteria (8).

- disease started when the patient was 40 years old or less
- claudication in an extremity
- weakened pulse in one or both of the brachial arteries
- more than 10 mmHg difference in systolic blood pressure between the two upper extremities
- audible bruit over one or both subclavian arteries or abdominal aorta
- narrowing or obstruction in the aorta, its main branches or large vessels in proximal parts of upper or lower extremities which have been confirmed angiographically (and therefore, the atherosclerosis or fibromuscular dysplasia has been ruled out)

Activity of the disease (according to "modified" NIH guideline (8–10):

- systemic signs and symptoms such as fever or arthralgia
- increased ESR or CRP levels
- signs of vascular insufficiency (pulses of variable intensity in the extremities or pulselessness, limb claudication)
- new lesion in serial vascular imaging in previously normal vessels

Exclusion criteria included the following:

- other connective tissue disorders
- infectious diseases such as tuberculosis
- Ehlers–Danlos syndrome or Marfan syndrome
- patients with profiles that were not complete regarding the necessary information

- patients who were not reluctant to take part in the study
- patients without ECG, chest X-ray, echocardiography, or angiography

Important laboratory tests including ESR at the time of diagnosis and its fluctuations, including ESR after remission of acute phase symptoms, white blood cell (WBC) count at the time of diagnosis, rheumatoid factor (RF), anti-nuclear cytoplasmic antibody (ANCA), and purified-protein derivative (PPD) test results were investigated. Symptoms and signs of complications were examined at intervals of three to six months after TA diagnosis.

Remission was defined as the disappearance of clinical and laboratory findings of active disease and absence of any new vascular lesion. Stable remission generally lasts for at least six months with the patient on a daily prednisolone dose of less than 10 mg.

TA angiographic classification is described as follows:

- Type I: involvement of aortic arch-cervicobrachial
- Type II: involvement of thoracoabdominal aorta
- Type III: peripheral involvement (descending aorta, abdominal aorta, and/or renal vessels)
- Type IV: combination of types I, II, and III

The results of physical examinations and laboratory/imaging studies of the patients recorded included blood pressure at the time of diagnosis, fundoscopy, cardiac sounds, assessment of bruit and pulses, chest X-ray and ECG. All the patients were administered prednisolone and azathioprine daily.

This study was performed according to the Declaration of Helsinki and all the participants provided their informed consent and permission to access their medical records. The study was also approved by the ethics group of Shad Beheshti University.

Data were entered and analysed using Statistical Package for the Social Sciences (SPSS) software (Version 16). We describe variables using frequencies and percentages. Chi-square test was used to analyse the association between categorical variables. *P* value less than 0.05 (two-sided) was considered as statistically significant.

Results

From the 25 patients diagnosed with TA, 15 had the criteria to be included in the study. Ten patients were excluded from our study because two patients did not have complete laboratory test results, five patients did not undergo follow-up angiography and computed tomography (CT), three patients stopped the recommended treatment and switched to traditional therapeutic options such as herbal medicine. Eleven (73.3%) out of 15 were females and four (26.6%) were males. The age range of the patients at the time of diagnosis was 19–51 years with a median age of 36 years. The time interval between the beginning of symptoms and diagnosis of TA was 6 months to 2 years with a median of 14 months.

Clinical manifestations

As seen in Table 1, the most frequent symptoms at the time of diagnosis were systemic manifestations such as fever in 10 patients (66.6%), and fatigue or malaise in 7 patients (46.6%). According to the modified National Institute of Health (NIH) criteria (8–10), 56.0% of the patients were in the acute phase of the disease. The most commonly observed auscultatory findings were subclavian bruit [13 patients (86.6%)] and carotid bruit [7 patients (46.6%)].

Lack of pulse was observed in 11 patients (73.3%) at the time of diagnosis and 13 patients (86.6%) had upper extremity claudication at the time of diagnosis. Eight patients (53.3%) had hypertension and two of them (13.3%) had suffered a myocardial infarction. An aortic regurgitation murmur was found in two patients (13.3%). Echocardiography revealed aortic regurgitation in 11 patients (73.3%).

Five patients (33.3%) had abnormal funduscopy results. All of the patients had negative history of tuberculosis. Seven patients (46.6%) were smokers.

Laboratory results

As shown in table 2, ESR range was 30–125 mm/h with a median of 88 mm/h. Nine patients (60.0%) had an elevated ESR of more than 35 mm/h at the time of diagnosis. Elevated CRP levels of more than 9 mg/L were found in eight patients (53.3%). Five patients (33.3%) had leukocytosis with a WBC count of more than 9000. All the patients had negative results for RF, ANA and ANCA. Six patients (40.0%) had purified-protein derivative PPD > 10 mm. Two patients (13.3%) were hypercholesterolaemic and were undergoing treatment.

Table 1: Clinical manifestations in 15 patients with TA

TA feature	n (%)
Systemic manifestations	
Fever (> 37.5 °C)	10 (66.7)
Fatigue/Malaise	7 (46.7)
Arthralgia	4 (26.6)
Weight loss	3 (20.0)
Cardiovascular	
Chest pain/Dyspnea	5 (33.3)
Subclavian bruit	13 (86.7)
Carotid bruit	7 (46.7)
Abdominal bruit	6 (40.0)
Femoral bruit	3 (20.0)
Upper-limb claudication	13 (86.7)
Pulselessness	11 (73.3)
Aortic regurgitation murmur	2 (13.3)
ECG findings	
Normal sinus rhythm	15 (100.0)
LVH	4 (26.6)
Chest X-ray findings	
Normal	13 (86.7)
Cardiothoracic ratio > 50%	2 (13.3)
Abnormal funduscopy	5 (33.3)
Hypertensive	8 (53.3)
Presence of Myocardial Infarction	2 (13.3)

Table 2: Laboratory findings in 15 patients with TA

Finding	n (%)
ESR (30–125) median 88 mm/1h	15 (100.0)
ESR > 35	9 (60.0)
CRP > 9	8 (53.3)
WBC > 9000	5 (33.3)
PPD > 10 mm	6 (40.0)
Positive RF	0 (0)
Positive ANA	0 (0)
Positive ANCA	0 (0)

Angiographic findings

As shown in Table 3, four patients (26.6%) had type I, three (20.0%) had type II, one (6.6%) had type III and seven (46.6%) had type IV TA. Two cases of myocardial infarction occurred in patients with type I involvement, both of which were non-fatal. All four patients in type I had hypertension, one of which had aortic regurgitation needing valve replacement 12 months after diagnosis.

All three patients of type II had hypertension, and ECG revealed signs of left ventricular hypertrophy (LVH) in two of them. Two of these patients had involvement of renal vessels and an abdominal bruit was detected in both of them. Both had been under anti-hypertensive medications and none met the criteria for undergoing renal vessels angioplasty.

In the only patient with type III involvement, the abdominal aorta was involved and there was no lack of pulse or hypertension or any other complication.

In type IV, the most commonly observed type, severe complications included ophthalmologic problems, lack of pulse and/or claudication. One patient had hypertension and there was one case of CVA with right hemiplegia, two years after diagnosis in a 41-year-old man.

In five patients, coronary angiography was performed because of cardiac symptoms. One patient was a 22-year-old male smoker and the other four were females without coronary risk factors (excluding hypertension), all of which were under the age of 50. Three out of these five patients had significant coronary lesions which led to myocardial infarction (MI) in two patients. Percutaneous trans luminal coronary angioplasty PTCA and stenting was performed for all three patients.

Regarding vascular lesions, the most common finding in angiography was stenosis in 60.0% patients, followed by occlusion in 46.7%, dilatation in 33.3%, and aneurysm in 26.6% (Table 4). Nine patients (60.0%) had lesions both below and above the diaphragm and 26.0% had isolated lesions above the diaphragm. All four types of lesions increased in follow-up angiography because of prolonged duration of the disease. Dilatation and aneurysm have only been observed in patients who had a history of disease for at least 3 years (Figure 1).

There was an association between the location of vascular lesion and clinical manifestations. Hypertension was more commonly found in patients with renal artery stenosis (86.0% vs 34.0%, $P < 0.001$). No significant association was

Table 3: Angiographic findings in 15 patients with TA

Classification	n (%)
Type I	4 (26.6)
Type II	3 (20.0)
Type III	1 (6.6)
Type IV	7 (46.7)
Involvement of vessels	
Left carotid artery	4 (26.6)
Left subclavian artery	7 (46.7)
Right carotid artery	3 (20.0)
Right subclavian artery	4 (26.6)
Descending aorta	6 (40.0)
Renal artery	2 (13.3)
Left femoral artery	3 (20.0)
Right femoral artery	1 (6.6)
Pulmonary artery	2 (13.3)
Coronary artery	3 (20.0)

Table 4: Frequency of stenosis, occlusion, dilatation, and aneurysm in 15 patients with TA

Lesion type	n (%)
Stenosis	9 (60.0)
Occlusion	7 (46.7)
Dilatation	5 (33.3)
Aneurysm	4 (26.6)

found between hypertension and dilatation or aneurysm.

Six patients (40.0%) underwent pulmonary angiography because they had pulmonary symptoms. In two of these patients, occlusive lesions were found in pulmonary artery.

According to Table 3, the most commonly involved vessel was the left subclavian artery (7 patients; 46.6%). Other vessels involved were descending aorta (6 patients; 40.0%), left carotid artery (4 patients; 26.6%), right subclavian artery (4 patients; 26.6%), right carotid artery (3 patients; 20.0%), left femoral artery (3 patients; 20.0%), coronary artery (3 patients; 20.0%), renal artery (2 patients; 13.3%), pulmonary artery (2 patients; 13.3%), and right femoral artery (1 patient; 6.6%).

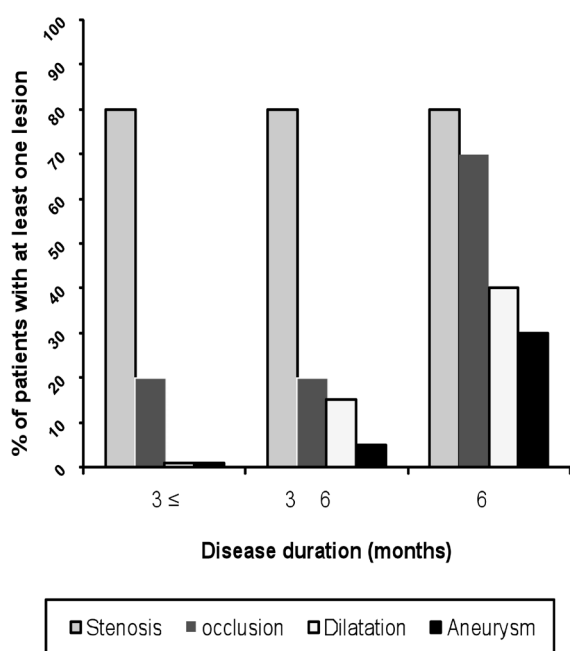


Figure 1: Percentages of patients with at least one lesion in three different time period (before 3 months, between 3 and 6 months and after 6 months).

Discussion

In this study, female-to-male ratio was 1.27:1. This ratio has been reported to be 1:1.5–1:9 in different studies (5,12,13,15,19–21). The median age of patients at the time of diagnosis was 36 years (range: 19–51) (12,31,15, 19–21,24–26) and the median interval between the beginning of symptoms and diagnosis of TA was 14 months (range: 6 months–2 years), which is comparable to other studies (16). This probably shows that in this setting, diagnosis of TA patients is in line with other settings worldwide in terms of the delay between onset and diagnosis. Considering a higher prevalence of TA in Asia and a relatively strong association of this disease with the female gender (1), a possible role for genetic factors could be suggested. In a study from Greece, an association has been reported between HLA-B52 and TA as this HLA was observed in 37.0% of TA patients (21). Sheikhzadeh et al., (15) also reported an association between HLA-B5 and TA.

Among the signs and symptoms, the most common finding was fever. Other studies have also reported this to be most common finding (23). Stenosis was the most common angiographic finding in our study (60.0% of patients) (21).

According to the modified NIH criteria (8–10), 44.7% of patients are diagnosed to be in the active phase of the disease. This was 56% in our study. However, we considered ESR and CRP as the indicators of activity, which is based on the reports from other studies. These indicators might not be sensitive enough for the detection of disease (21).

Most common auscultatory finding of this study was bruit (86.0% of patients). The most common location of bruit was over the subclavian artery. In a study by Maksimowicz et al, in 2007 (18), bruit was found in 53.0% of patients and in a study by Waern Au et al, the most common artery involved was the subclavian artery (13). In two other studies, it has been reported to be present in 77.0% and 89.0% of the patients (20,15).

The involvement was found to be on left side more than on the right side. It is in line with Ishikawa's theory stating that TA lesions would begin in left subclavian artery and then extend to other locations (10).

Hypertension was found in 53.3% of our patients. Hypertension has reported to be 72.0%, 58.0%, 72.0%, 43.0%, and 4% in different studies from Italy, Iran, India, Turkey, and Tunisia, respectively (5, 15, 19, 20, 26). Hypertension has been associated with renal artery stenosis in 13.3% of patients in our study. This association has been found in 18.7% of patients, in a study from Thailand (14), 35.8% in a study from Iran (15), 26.0% in a study from Turkey (20) and 24.0% in a study from Southern Tunisia (22).

In five patients of our study, angiography was performed because of persistent chest pain; of which three had significant coronary lesions and underwent PTCA. Two cases of MI occurred during follow-up (incidence of 13.3%). Coronary involvement has been reported to be 0% and 7.6% in two studies from Tunisia and Iran, respectively (26,15).

Two of our patients had aortic insufficiency and one of them required valve replacement 12 months after diagnosis. In the study of Sheikhzadeh et al., (15), 15 of 78 patients had aortic insufficiency and four required valve replacement therapy. A high ratio of aortic valve involvement has been reported in a study from Turkey (33.0%) (20).

One of the complications of TA is the involvement of the pulmonary artery, which can mimic pulmonary embolism. In a previous study from Iran, 20% of patients had pulmonary artery involvement (15). This has been 12% in another study (20). In a study from Tunisia, no patient had

pulmonary artery involvement (22). In this study, it was reported to be 13.3%. The investigators of this study believe that not performing pulmonary angiography routinely for all TA might have resulted in underestimation of this complication.

In the study of Sheikhzadeh et al., (15), pericardial effusion was found in 2% of TA patients. None of the patients showed signs of pericardial effusion in our study. Sheikhzadeh et al., (15) reported common ophthalmopathies such as retinal venous congestion, micro aneurysms and arterio-venous shunts in 6% of their patients. Abnormal fundoscopic results were observed in 33.3% of our patients.

In line with another study (15), results of RF, ANA and ANCA tests were negative in our study. Sheikhzadeh et al., (13) had a 34.6% rate of PPD positivity. This was reported to be 48%, 81% and 20% in other studies (5, 13, 19). In our study, 40.0% of patients had a positive PPD test result, suggesting an association between prior mycobacterium tuberculosis exposure and TA. No patient in our study had active tuberculosis, similar to a study in Tunisia (22).

Angiography is the diagnostic gold standard (1,12,13). Most common angiographic type in our study involved the left side. This is in line with studies from Tunisia (26) and Iran (15), in which the most common type has been type IV and the most common involvement location has been the left subclavian artery. However, in other studies from Tunisia, Korea and Turkey, the most common angiographic type was type I (22,17,20) and in another study from Thailand, abdominal aorta was reported as the most common location involved (14).

In summary, we have described the clinical manifestations and complications of TA along with their laboratory and angiographic findings. The strengths of our study are the following; this study is multi-centric, including the assessment of complications in a thorough manner. The authors do believe that this study bears some limitations such as a small sample size, being descriptive and retrospective, and not taking patients' medications into consideration. In future, cohort or randomised controlled trials with larger sample sizes will be designed to investigate different therapeutic approaches and their possible effects on the occurrence of complications in TA. Considering the fact that TA commonly affects young people, especially women of child-bearing age, it is hoped that the knowledge and prevention of complications can result in helping these patients and potentially reduce the impact of the

disease with proper diagnosis and management.

Conclusion

The most common clinical, laboratory and angiographic findings in a decreasing order of occurrence were fever, increased ESR, and stenosis, respectively. Because of dangerous consequences of this disease, attention to fever and increased ESR specially in young women may be helpful for physicians to prevent diagnosis delay. Our data is important as the baseline findings of the profiles of TA patients in Iran and will be useful in future research projects concerning this disease in this region.

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Conflict of Interest

None.

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None.

Authors' contributions

Conception and design, analysis and interpretation of the data and administrative, technical or logistic support: DN

Drafting of the article, critical revision of the article for the important intellectual content collection and assembly of data: PN

Final approval of the article and obtaining of funding: SS

Provision of study materials or patient and statistical expertise: JA

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