Original Article

Clinical Characteristics of Takayasu Arteritis: A Retrospective Study from a Tertiary Care Hospital in North India

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Abstract

Introduction: Takayasu's arteritis (TA) is a granulomatous vasculitis of the large vessels, mainly involving the aorta and its branches. The disease has diverse manifestations across various ethnic populations. The epidemiological profile of TA has not been well established in India, with existing studies demonstrating varied clinical findings. **Materials and Methods:** In this retrospective, hospital record-based study, 30 TA patients, meeting 1990, American College of Rheumatology criteria for TA, were included. The study intended to characterize the demographic profile, clinical characteristics, laboratory parameters, imaging findings, and management profiles of TA, amongst patients presenting to the rheumatology outpatient department of a tertiary care hospital in India. **Results:** The mean age at presentation was 26.4 ± 11.4 years. The male to female ratio was 1:5. The mean duration from onset of symptoms to point of diagnosis was 8.7 ±5.7 years. Upper limb claudication was the most frequent symptom seen in 23/30 (76.7%) patients, followed by syncope in 12/30 patients (79%). The most common arteries involved were the subclavian artery, carotid artery and the renal arteries (counted together). Type 1 and Type V were the most common angiographic subtypes, each seen in ten (33.3%) patients. Methotrexate was the most frequently used conventional synthetic disease modifying anti-rheumatic drug (csDMARD) and was used in 27/30 (90%) patients. A total of five (16.7%) patients required biological DMARDs (bDMARD) in view of refractory disease, four patients received tocilizumab while one patient received infliximab. **Conclusion:** TA is a female predominant, large vessel vasculitis. The subclavian arteries, followed by the common carotid and the renal arteries, are the most common vessels involved. Tocilizumab is fast emerging as an effective bDMARD for disease control especially in csDMARD refractory cases.

Keywords: Left subclavian artery, North India, Takayasu Arteritis, Tocilizumab, Upper limb claudication, Large vessel vasculitis

Introduction

Takayasu arteritis (TA) is a large vessel vasculitis with predilection for the aorta and its branches. It was first described in 1908 by a Japanese ophthalmologist, Mikito Takayasu, who found micro aneurysms in the fundus and arteriovenous anastomoses while examining the retina of a 21-year-old female.[1] Even though TA has a global distribution, it is more commonly seen in Asia, as compared to Europe and America. It is a fairly uncommon disease, with a recent study citing the prevalence of TA at 22 per million in Europeans, as compared to 78.1 in Asians and 108.3 in Africans.[2] It remains the primary cause of reno-vascular hypertension in the South East Asian countries.[3] Various factors have been implicated in the etiopathogenesis, however, the most prominent being the role of the gamma delta T-lymphocytes that release perforin on recognizing an unknown antigen in the aortic vessel wall, thereby causing vascular injury.[4]

TA mainly affects young women in the age group of 10–40 years.[5] The onset is sub-acute in the majority of the patients; however, a sudden onset subtype has been described by Ishikawa in 24% of the patients, in his study.[6] Clinical features include upper and lower limb claudication, hypertension, carotidynia, and angina. Constitutional symptoms in form of fever, malaise, night sweats, arthralgia, weight loss, and myalgia have also been described.[7] A widely

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followed angiographic classification from 1994, classifies TA into six subtypes[8] [Table 1]. The disease presentation can vary with subtype, ethnicity, and geographical location. For example, Japanese patients have a predominant disease of the aortic arch and its branches, whereas in Indian patients, the renal arteries are involved. African patients, on the other hand, have a predominant lower abdominal aorta involvement.[9]

Data on TA from Indian studies are heterogeneous, with different studies demonstrating predominance of different subtypes. We herein, attempted to investigate the clinical, radiological, and management profile of patients with TA from a tertiary care hospital in Northern India.

Materials and Methods

Aims and objectives

To study the clinical features, laboratory parameters, imaging and management profiles of 30 consecutive patients classified as TA as per the 1990, American College of Rheumatology (ACR) criteria[5] reporting to the rheumatology outpatient department of a tertiary care hospital in Northern India.

Study design

This was a retrospective, hospital record-based study.

Study setting

The study was carried out at a tertiary care hospital in Northern India.

Study population

Thirty patients with the diagnosis of TA, as extracted from the hospital records were included in the study.

Inclusion criteria

All patients diagnosed as TA as per the 1990 ACR classification criteria for TA[5] were included in the study.

Study period

Hospital records of TA patients from January 1, 2013, to December 31, 2016, were studied and relevant data extracted.

Study variables

The demographic profile including age at onset, time to diagnosis, gender, modes of clinical presentation, laboratory parameters including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, and liver and renal function tests were obtained and recorded in a predesigned information sheet in the Microsoft excel. Data pertaining to angiographic findings of all patients (whether the patient underwent computed tomography angiography (CTA) or magnetic resonance angiography (MRA) for the classification of disease as per anatomy) and ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) (used for the estimation of disease activity) was also extracted. ESR and CRP had been estimated by the Westergren method and nephelometry (Beckmann Coulter, Brea, California, United States), respectively. Reference range for ESR was 0–15 mm/h (male) and 0–20 mm/h (female), while the normal values for CRP was <8 mg/L. CTA had been performed using a Multidetector Row CT Scanner (Phillips 256 CT Amsterdam, Netherlands) while MRA had been performed using a 1.5 Tesla whole-body (WB) magnetic resonance imaging (MRI) Machine (Siemens, Erlangen, Germany) using the intravenous administration of Dotarem (Gadoterate meglumine, *Guerbet LLC, Bloomington, USA*). ^{18}F-FDG-PET had been performed on GE Discovery PET/CT scanner (GE healthcare, Chicago, IL, USA).

Statistical analysis

Descriptive analysis was done using mean and standard deviation for continuous variables and frequency and percentages for categorical variables. The data were collected and compiled on Microsoft excel version 2019 and analyzed using Stata Corp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP.

Ethics approval

The institutional ethics committee approved the study, IEC Number-EC/2020/198.

Results

The mean age at the presentation was 26.4 ± 11.4 years. The female:male ratio was 5:1. The mean duration from the onset of symptoms to confirmation of the diagnosis was 8.7 ± 5.7 years.

Table 1: Angiographic classification of Takayasu arteritis[7]

Classification	Vessels involved
Type I	Only the branches of the aortic arch
Type IIa	Ascending aorta, aortic arch, and its branches
Type IIb	Affects ascending aorta, aortic arch and its branches, and thoracic descending aorta
Type III	The descending thoracic aorta, the abdominal aorta and/or the renal arteries. The ascending aorta, the aortic arch and its branches are not affected.
Type IV	Involves only the abdominal aorta and/or renal arteries
Type V	Combined features of Type IIb and IV

Table 2: Involvement of different arteries (*n*=30)

Branch involved	*n* (%)
Left subclavian	23 (77)
Left common carotid	13 (43)
Right subclavian	10 (33)
Arch of aorta	9 (30)
Abdominal aorta	7 (23)
Thoracic aorta	6 (20)
Left renal artery	6 (20)
Right renal artery	5 (17)
Right common carotid	4 (13)
Coeliac artery	4 (13)
Brachiocephalic	3 (10)
Vertebral artery	3 (10)
Ascending aorta	2 (7)
Femoral artery	1 (4)

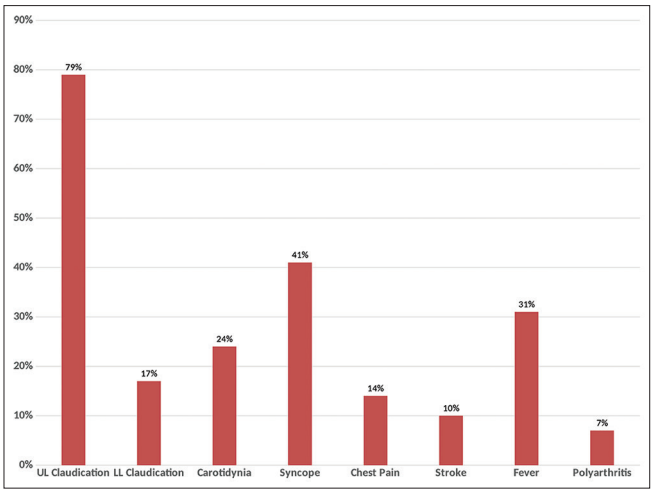

Figure 1: Frequency of different symptoms at the onset. UL- upper limb, LL- lower limb

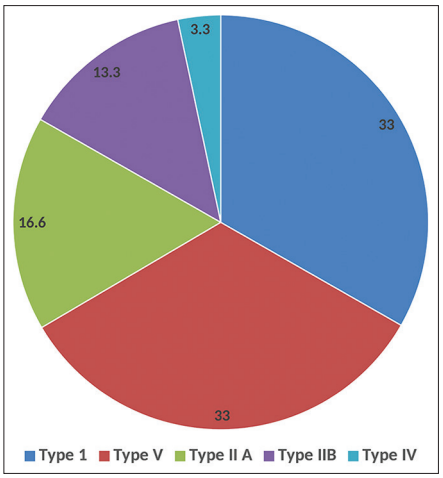

Figure 2: Distribution of different angiographic subtypes. The figures indicate percentages

The most common symptoms at presentation were upper limb claudication and syncope seen in 23/30 (79%) and 12/30 (40%) of the patients, respectively. Hypertension was present in eight (26.6%) patients, whereas three (10%) patients had a history of ischemic stroke. Details of symptoms are depicted in Figure 1. Ten (33%) patients had systemic symptoms in the form of fever, polyarthralgia, fatigue, and weight loss.

Analysis of laboratory parameters revealed that the mean ESR was 50 ± 37 mm. 24/30 (80%) patients had ESR ≥20 mm. The mean CRP was 30 ± 30.2 mg/L. Anemia was present in 18/30 patients (60%). None of the patients had valvular regurgitation on echocardiography.

25/30 (83%) patients underwent CTA as the first choice of imaging and five (17%) underwent MRA. Details of vessel involvement are given in Table 2. The most common angiographic types were Type 1 and Type V (Both 10/30 [33.3%] each). Type 3 was not reported in our study [Figure 2]. 12/30 (40%) of the patients underwent ^{18}F FDG PET-WB scan to assess for disease activity at the time of the diagnosis in patients who gave consent. Two (6.66%) showed evidence of activity on FDG PET. One case had moderate FDG avidity seen in the wall of ascending aorta, arch of the aorta, and right common carotid artery, and the second case had diffuse circumferential intimal mural thickening of the aorta and right brachiocephalic trunk. Both these patients had markedly elevated ESR, 110 mm and 145 mm, respectively. Similarly, CRP was also markedly elevated in these patients.

All patients required glucocorticoids for disease control. Methotrexate (MTX) was used as the first-line conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in 27/30 (90%) patients, whereas three (10%) required a switch to mycophenolate mofetil (MMF) in view of having progressive disease, while on MTX. Four (13.5%) patients received tocilizumab at 8 mg/kg every month (a total of 11, 6, 6, and 3 doses were required to achieve disease remission) and one patient received a tumor necrosis factor alpha inhibitor, infliximab, at a dose of 5 mg/kg at 0, 2, and 6 weeks and then every 2 months (a total of 8 doses were required), to achieve disease remission.

Discussion

TA is a large vessel, chronic, granulomatous vasculitis affecting all the three layers of the large vessel wall, especially the aorta and its major branches. It causes vascular scarring leading to stenosis and occlusion, manifesting with the symptoms of organ hypoperfusion. Various criteria have been formulated for the diagnosis like the Ishikawa,[6] ACR,[5] and the Indian criteria by Sharma *et al*.[10] with sensitivity and specificity of 60.4% and 95%, 77.4% and 95%, and 92.55% and 95%, respectively. We used the ACR criteria in our study.[5]

Our study revealed a female preponderance with a male:female ratio was 1:5. These findings were similar to the studies from the West (1:9),[2] as well as from Japan (1:3).[11] Similar results were also shown by Mondala *et al*. in their study on TA, from Eastern India.[12] However, other studies from India have differed and shown an almost equal occurrence in males and females.[3,13,14] The probable reason for this could be a heterogeneity of the Indian population. The average age at the onset of TA in India is in between 20 and 30 years (Mean age 27.3 years).[15] Our study presented similar findings, with a mean age at the diagnosis being 26.4 years.

In the present study, the most common symptoms at the presentation were upper limb claudication in 79% and syncope in 40% of the patients, which are similar to the findings by Salkar *et al*.[13] Majority of the patients presented with hypertension, headache, and breathlessness in a study by Jain *et al*.[3] The probable reason for this could be that our set of patients had predominant subclavian artery involvement. Dabague and Reyes,[16] in their study showed that fever was present in 44% of the cases, which was in consonance with the findings of our study.

In our study, on angiography, the subclavian arteries were the most commonly involved, followed by the carotid, and the

Table 3: Comparison of the present study with the five different studies from India

Characteristics	Sagdeo *et al*.[18] (Western India)	Sharma *et al*.[17] (Western India)	Jain *et al*.[14]	Salkar *et al*.[13] (Central India)	Mondala *et al*.[12] (Eastern India)	Present study (North India)
Number of patients	48	30	30	33	71	30
Mean age at presentation	34.2	24.7	30.5	29	25.66	26.4
Female: male ratio	2.69:1	1.2:1	1.14:1	1.75:1	4.8:1	5:1
Disease duration at diagnosis	NA	NA	NA	NA	11.8 months	8.7 (1 month–8 years)
Systemic symptoms	41.6%	23%	20.2%	30.3%	35.93%	33%
Stroke	14%		16.6%	15.15%	NA	10%
Upper limb claudication	NA	6.6%	NA			79%
Lower limb claudication	NA	6.6%	NA	66.67%	50.76%	17%
Mean ESR	51	NA	NA	NA	45.04	50
Subclavian artery involvement	NA	16.6%	26.6%	NA	70.76%	80%
Predominant angiographic type	Type V	Type III (50%)	Type III (60%)	Type IV (63.64%)	Type I (47.7%) Type V (38.5%)	Type I (33.3%) Type V (33.3%)
Renal artery involvement	10%	76.6%	73.2%	NA	27.69%	24%
FDGPET performed	70%	NA	NA	NA	NA	40%
DMARD used	MTX (58%)	AZA	NA	NA	NA	MTX (90%)
Biological DMARD used	Nil	Nil	NA	NA	NA	Tocilizumab

AZA: Azathioprine, DMARD: Disease-modifying anti-rheumatic drug, FDGPET: Fluorodeoxyglucose positron emission tomography, MTX: Methotrexate, NA: Not applicable

renal arteries (left and right counted together), in that order. Other studies from India have documented different patterns of involvement of arteries. A study by Sharma *et al*.[17] showed the involvement of renal arteries in 76.6% and left subclavian artery in 16.6% of the cases. While the study by Jain *et al*., conducted amidst the Gujrati population, observed that the abdominal aorta was most commonly involved (71% patients).[14] Type III was the most common angiographic pattern in both these studies, whereas the most common angiographic patterns in our study were Type 1 (33.3%) and Type V (33.3%). Here, our study was in consonance with the studies by Sagdeo *et al*.[18] from Western India and Mondala *et al*. from Eastern India.[12] The probable reason for this could be that India is a vast country with diverse populations of different ethnicities, with lots of intermixing of communities, in all regions of the country. A comparison of our study with the other five major studies from India is depicted in Table 3.

In the present study, 83% of the patients underwent CTA while 17 % underwent MRA for ascertaining anatomy. The choice of imaging in our study was influenced by personal choice, availability, and expertise of the radiologist. Both imaging techniques have their own drawbacks, in correctly identifying the vessel wall inflammation.[19] Postcontrast vessel wall enhancement during CTA has been associated with disease activity, but this is not continually genuine, and variable results have been found.[20] In a prospective study using electrocardiogram-gated and edema-weighted MRI technique for TA patients, active arterial inflammation was not reliably detected by MRI and thus raising the question that vessel wall edema might not actually represent inflammation.[19] Nevertheless, the rapid advancement in MRI techniques indicates that this mode of noninvasive imaging is fast emerging as the gold standard, in assessing disease activity.

In the present study, ^{18}F-FDG PET-WB metabolic imaging was done in 40% of the cases to assess the disease activity at the time of diagnosis. There is no unanimously established method for quantification of FDG uptake. Classically, the vascular uptake in the subclavian arteries, carotids, and the aorta, is matched with the liver and spleen to produce a standardized uptake value for different vascular territories.[21,22] The linear uptake seen in the vessel wall of TA patients with the active disease might be reduced by DMARD's;[21-23] however, in patients in clinical remission with normal ESR and CRP levels a persistent low-grade uptake could be seen.[23] It would be very challenging to establish the exact cause of low persistent linear uptake in the vessel wall due to the lack of adequate biopsy material. It might be because of residual low-grade inflammation in the vessel wall or due to vascular wall remodeling. Further prospective studies are required to validate this fact. Therefore, the findings of FDG-PET need to be interpreted very carefully in the setting of low-level persistent uptake, and instead of escalating treatment in this setting, it is better to observe and follow up the patient.

The outcome measures in TA have gained importance in the recent times with the advent of the Indian Takayasu Clinical Activity Score (ITAS2010).[24] Since ours was a retrospective study, the same scoring was not carried out in our patients. In our study, patients received maintenance immunosuppression with MTX or MMF; however, five patients had refractory disease despite csDMARDs, and required biological DMARDs (bDMARDs) (infliximab and tocilizumab). In the Tocilizumab group, the average doses required were three

to six, with one patient requiring 11 doses for achieving remission. The glucocorticoids remain the first-line option for TA, but most of the patients will deteriorate with the withdrawal of glucocorticoids. A recent meta-analysis showed that a large majority of the patients will require an additional immunosuppressive drug to attain clinical remission when the dose of glucocorticoid is reduced.[25] MTX, azathioprine, MMF and cyclophosphamide are the available second-line agents.[26,27] Tocilizumab is an anti-interleukin-6 (IL-6) receptor blocker. It binds to membrane-bound and soluble IL-6 receptors and thus averting IL-6 attachment to its receptor and further signaling.[28] The serum levels of IL-6 relate to the activity of the disease.[29] This signifies that IL-6 has a role in the pathogenesis of TA and a possible therapeutic role for Tocilizumab. A recent study showed that till 2018, Tocilizumab had been used in 105 TA patients globally, and out of them, 85.7% of the patients achieved clinical remission and 65.2% achieved radiological response.[30]

Our study had a few strengths; it is among the few Indian studies to have used ^{18}F FDG PET-WB metabolic imaging for the assessment of disease activity in TA, and also to have assessed the pattern of bDMARD use, albeit there were few limitations arising out of a small sample size. Furthermore, the study population was not wholly representative of the Indian population as a whole, because our hospital primarily caters to a North Indian clientele. We did not do ITAS scoring for outcome assessment and our patients did not undergo follow up FDG PET-WB, to look for disease responses to immunosuppression.

Conclusion

TA is a large vessel vasculitis predominantly involving young females. MRA and CTA are both useful in ascertaining anatomical involvement, with MRA holding an edge. The angiographic subtypes and clinical presentations vary in the different parts of India. ^{18}FDG PET is an emerging modality for assessing disease activity in TA. Early use of bDMARDs such as tocilizumab has helped in achieving better disease control, thereby reducing morbidity.

Financial support and sponsorship

Since the study was conducted in a government hospital, the biologics used in this study were provided to the patients free of cost, and all laboratory investigations were carried out in the hospital laboratory.

Conflicts of interest

There are no conflicts of interest.

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