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EDITORIAL

Takayasu's Arteritis: An Indian Perspective

Introduction

Takayasu's arteritis (TA) is a chronic vasculitis involving mainly the aorta and its branches, as well as the pulmonary and coronary arteries. The classical definition of Takayasu's Arteritis is that of chronic, progressive, inflammatory, occlusive disease of the aorta and its branches.

Epidemiology

Although TA has a worldwide distribution, it is observed frequently in Asia than in North America. TA is the most common cause of renovascular hypertension in India, China, Korea, Japan and other countries of South East Asia.[1,2]

Aetiology

The aetio-pathogenesis of the disease remains enigmatic. An infectious etiology has been considered with one series reporting active tuberculosis infection in 60% of autopsy cases of non-specific aortitis.[3] Various mechanisms such as post-infective, autoimmune, ethnic susceptibility and a genetic predisposition have been postulated. Autoimmunity appears to be the most plausible mechanism. Both cellular and humoral factors are probably involved. Defective T lymphocyte regulation and anti-endothelial antibodies have also been implicated. A provocative hypothesis put forward by Kothari S.S. explores the possibility of BCG vaccination as a triggering factor for TA in a susceptible population.[4] A 65 M heat shock protein (HSP) which plays a role in vascular injury has been shown to be a component of both BCG and Mycobacterium tuberculosis.[4] Kinare SG *et al.* noted a high incidence of tuberculin positive skin hypersensitivity in patients of Takayasu arteritis.[5]

Several studies have proposed various human leukocytes antigen (HLA) associations, suggesting a genetic pre-disposition for the disease. The geographical incidence and the occasional familial occurrence also suggest the role of genetic factors. Takeuchi Y *et al.* demonstrated an association between Takayasu's arteritis and HLA-D gene at the genomic level.[6] Khraishi MM *et al.* in 1992, reported a negative association between this disease and HLA-DR 1, implying a protective association with Takayasu's arteritis.[7] The tendency for the disease to affect women of reproductive age has suggested a potential role for hormonal influences in the pathogenesis of Takayasu's arteritis. An association between the disease and specific HLA types A9, A10, B5, BW52, DHO, and DW12 in Japanese patients and B5 and B21 in Indian patients have been found.[8,9]

Diagnostic Criteria

In 1988, based on an analysis of 96 patterns Ishikawa proposed criteria for the clinical diagnosis of TA.[10] The criteria consisted of obligatory criteria of age less than 40 years. Two major criteria of left and right subclavian artery lesions and nine minor criteria include hypertension, a high erythrocyte sedimentation rate and arteriographic demonstration of lesions of different arteries. In addition to the obligatory criterion, the presence of two major criteria or one major plus two or more minor criteria, or four or more minor criteria suggests a high probability of TA. The criteria have a sensitivity of 84% in patients of TA.

In 1990, the American College of Rheumatology suggested a set of criteria for the diagnosis of Takayasu arteritis.[11] The criteria consist of (a) age <40 years (b) claudication of an extremity, (c) decreased brachial artery pulse, (d) >10 mmHg difference in systolic pressure between arms, (e) a bruit in subclavian arteries or aorta and (f) angiography evidence of narrowing or occlusion of the aorta, its primary or proximal branches. Presence of three of the six criteria is required for the diagnosis. These criteria have a 90.5% sensitivity and 97.8% specificity.

Sharma *et al.* in 1995 suggested certain modifications in Ishiwaka's diagnostic criteria.[12] These modifications included (a) removal of the obligatory criteria of age, (b) the characteristic signs and symptoms being made one of the major criteria, (c) removal of

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age from defining hypertension, (d) deletion of the absence of aorto-iliac lesion from the ninth minor criteria and (e) an addition of a tenth minor criteria of coronary artery lesion in patients younger than age 30 years in the absence of risk factors such as hyperlipidemia, diabetes mellitus or any other known risk factor. The presence of two major or one major and two minor criteria or four minor criteria should suggest a high probability of TA (Table 1). These modified criteria seemed more sensitive for the diagnosis of TA in a series of 106 Indian patients with clinically and angiographically proven TA (Table 2).[13]

Imaging Findings

Four basic arteriographic patterns are observed in patients with Takayasu arteries[14]:

- Varying degree of aortic and arterial narrowing
- Complete occlusion
- Fusiform or saccular aneurysm
- Irregular contour of aortic wall

The most frequent finding is a localized narrowing or irregularity of the aortic wall. The narrowing may progress to significant coarctation and occasionally total occlusion of aorta or its major branches.

The main and large pulmonary arteries are also affected as a part of generalized arteritis, with arteriography revealing a paucity of the pulmonary vessels in lobar or segmental distribution. According to the angiographic classification proposed by Ueda *et al.* and modified by Lupi HE *et al.* based on changes of vascular lumen, namely stenosis, occlusion, wall irregularity or aneurysm; angiographic findings can be classified into four types.[15,16]

- Type I is limited to the aortic arch and its branches.
- Type II affects the descending thoracic and abdominal aorta.
- Type III is extensive form involving the arch and the thoracic and abdominal aorta.
- Type IV is designated to those cases with pulmonary involvement in addition to the features of type I, II, or III.

Pre-contrast transverse CT images reveal a high attenuation wall of variable thickness and of variable mean CT number in the aorta and major branches.[17] CT angiogram demonstrates circumferential wall thickening of 1–4 mm thickness. The thickened aortic wall may be enhanced inhomogeneously during the arterial phase. The delayed phase images reveal

Table 1. Modified diagnosis criteria for Takayasu arteries[12]

Three major criteria	
Right mid subclavian artery lesion	The most severe stenosis or occlusions present in the mid portion from the point 1 cm proximal to the vertebral artery orifice determined by angiography.
Right mid subclavian artery lesion	The most severe stenosis or occlusions present in the mid portion from the right vertebral artery to the point 3 cm distal to orifice determined by angiography.
Characteristic signs and symptoms of at least one-month duration.	These include limb claudication, pulselessness or pulse difference (>10 mmHg systolic blood pressure difference in limb), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea or palpitations.
The minor criteria	
High ESR	Unexplained persistent high ESR >20 mm/hr (Westergreen) at diagnosis or presence of the evidence in patient's history.
Carotid artery tenderness	Unilateral or bilateral tenderness of common carotid arteries on palpation. Neck muscle tenderness is unacceptable.
Hypertension	Persistent blood pressure in brachial >149 mmHg, or popliteal >160/90 mmHg by auscultation or Doppler echocardiography or angiography.
Aortic regurgitation or Annulo-aortic ectasia	By angiography or two-dimensional echocardiography.
Pulmonary artery lesion	Lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination on pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography.
Left mid common carotid lesion	Presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography.
Distal brachiocephalic trunk lesion	Presence of the most severe stenosis or occlusion in the distal third determined by angiography.
Descending thoracic aorta lesion	Narrowing, dilation or aneurysm, luminal irregularity or any combination determined by angiography: tortuosity alone is unacceptable.
Abdominal aorta lesion	Narrowing, dilation or aneurysm, luminal irregularity or aneurysm combination.
Coronary artery lesion	Documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus.

Table 2. Sensitivity and specificity for the various diagnostic criteria[14]

Criteria	Sensitivity	Specificity
Ishikawa	60.4	95
American College of Rheumatology	77.4	95
Sharma *et al.*	92.5	95

further mural enhancement of the aorta and its major branches with Takayasu arteries involvement. The most characteristic gross pathological features are marked thickness and rigidity of the wall due to fibrosis of all the layers- intima, media and adventitia.[17]

Clinical Features of Takayasu Arteritis

TA classically progresses through 3 stages:

- An early systemic illness usually associated with constitutional symptoms and fever.
- A vascular inflammatory phase.
- The inflammation settles down or burns out.

The clinical features that have been ascribed to Takayasu's disease are listed in Table 3, according to the system involved. In 1996, the American National Institute of Health Investigators reported that only 33 percent of their sixty patients studied had constitutional symptoms or fever, either at presentation or in the past, and 18 percent of the patients never evolved into a burned out stage.[18]

Management

Besides management of hypertension and its complications, steroids and immunosuppressive agents like methotrexate and cyclophosphamide are used to suppress disease activity. Response to therapy is faster and better in children with a higher rate of remission.[19] Anti-platelet agents like aspirin and dipyridamole have been used especially in patients with transient neurological symptoms. Role of intravenous immunoglobulins, recombinant IL-1 receptor antagonist, IL-4 and transforming growth factor β is yet to be established.

Percutaneous transluminal angioplasty (PCTA) is the commonest palliative procedure performed with a success rate varying from 56–80%.[20] All lesions are not amenable to PCTA and surgical bypass procedures become imperative when stenosis exceeds 70%.[21] Irrespective of the surgical procedures undertaken, the outcome appears to be favorable when the disease is quiescent. Surgical procedures are required for total aortic occlusion, severe aortic incompetence, critical central nervous system ischemia, aneurysms, renovascular hypertension, ostial lesions, tight stenosis, extensive renal segmental artery involvement, poorly functioning renal units, renal failure and, occasionally, in case of failure of angioplasty.

Surgery for TA should be deferred in the active phase of the disease, which is characterized by an increased ESR, increased C-reactive protein and symptoms of fever, malaise or pain over the major arteries, or signs of progressive vascular involvement on angiography as the chances of thrombosis increase. Surgery is often difficult in the active disease period due to more bleeding, friable tissue and the high chance of thrombosis.

Table 3. Clinical features of Takayasu's disease

Constitutional	Fever (40%), Weight loss (40–60%), Malaise (40–60%), Anemia (40%), Myalgias (40%), Arthralgias (40–60%), Arthritis (40%)
Vascular	Jaw claudication, Extremity claudication, Neurological features (60%) includes the following: Transient ischemic attacks, Hemorrhagic or ischemic stroke, Transient or permanent blindness, Headaches, Seizures, Subclavian steal syndrome.
Cardiac	Aortic regurgitation, Angina, Congestive heart failure (primary cause of death), Arrhythmias
Pulmonary	Pulmonary hypertension (often asymptomatic), Hemoptysis, Pleuritis
Renal	Mesangial proliferative glomerulonephritis with mesangial deposits of IgM, IgG, IgA and C3 (Most frequent), Membranoproliferative and crescentric glomerulonephritis, Renal amyloidosis
Dermatological	Ulcerated subacute nodular lesions, Papular erythematous lesions of hands, Erythema multiforme

Indian Scenario

The prevalence of Takayasu Arteritis in Indian patients has been reported in numerous studies. Sen *et al.* and Chhertri *et al.* have reported a female to male ratio of 1.58:1 in Indian patients.[21,22] Indian male patients with TA have a higher frequency of hypertension and abdominal aorta involvement while female patients have a tendency towards involvement of aortic arch and its branches.[23] The average age of the Indian patient presentation is in the third decade. The disease has been observed to present in second decade in Latin America, third decade in Japanese and fifth decade in Swedish patients.[24]

The majority of Indian patients had hypertension at the time of presentation and only 16% of patients had constitutional symptoms of fever weight loss and arthralgia.[25] Hypertension has been a predominant feature in most of the studies from India.[1,2,25] It commonly results from the involvement of renal arteries (involved in 20–90% cases in different series).[24,25] Kumar A *et al.* reported that for young patients with renovascular hypertension, the predominant cause was TA (69.4%).[26] Bilateral involvement of the renal arteries is common in patients with TA (60%).[26]

Kumar A *et al.* reported the presence of congestive cardiac failure in patients of TA.[26] It was related to hypertension and the possible involvement of

myocardium has also been described by Talwar *et al*.[27] The incidence of aortic regurgitation has been low (7–15%) in many series from India but Subramaniyan *et al.* have reported a higher incidence (24%).[24,25] Kasuya *et al.* have reported that patients with TA and HLA Bw52 antigen have a more severe left ventricular involvement.[28] In Japan, TA frequently involves the aortic arch and the branches arising from it. In contrast, abdominal aorta and its branches are frequently involved in Indian patients occurring in 79% of patients.[25,29]

Dhingra *et al.* had detected anti-aortic antibodies in patients with TA.[30] Sima *et al.* demonstrated anti-endothelial antibodies by enzyme linked immunoabsorbent assay.[31] Misra *et al.* have reported elevated titers of IgG anticardiolipin antibodies in 14 of 34 patients of TA.[32] They had also documented an elevated CD4+ subset of T lymphocytes in patients with TA.[33] An expansion of CD4+ : CD8+ ratio, a high basal protein kinase activity and a high intracellular calcium concentration has been observed.[33] These features suggested that the circulating lymphocytes in TA are in an activated state but the exact stimulus for activation still remains obscure. An increase in CD8 positive Tcell subsets, increased IgG and IgM immunoglobulin levels, and the presence of autoantibodies including ANA, ANCA, anticardiolipin and anti-beta 2GPI antibodies in TA patients. The strikingly positive responses to tuberculin, as well as the multi-test CMI also indicate exaggerated T cell responses and cell mediated immunity in Takayasu's arteritis.[34]

As most of Indian patients present in the chronic phase, steroid therapy has not been used very commonly, though it is being employed more frequently than in the past.[33]

Khalilullah *et al.*, Sharma *et al.* and Kumar *et al.* have reported a high success rate with percutaneous transluminal angioplasty of renal, subclavian and iliac artery lesions.[20,35,36] The clinical benefit of renal angioplasty was seen in 85% of TA cases.[26] However, re-stenosis occurred in 24.23% cases at a median follow up of 4.6 years.[26] In earlier studies of balloon angioplasty for TA, Tyagi *et al.* reported a re-stenosis rate of 25.8% in 31 renal units, whereas Sharma *et al.* reported re-stenosis rate of 20% in 40 patients.[37,38] Although re-stenosis is a common problem of PTRA for TA, repeat procedures have provided good results. In most angioplasty series of TA, tight ostial stenosis and longer renal artery stenosis length are associated with higher re-stenosis rates.

Conclusion

Takayasu Arthritis remains the commonest cause of renovascular hypertension in India. Better understanding of disease aetiology and pathogenesis is required for better outcomes in the future.

R. Parakh*, A. Yadav
Department of Vascular and Endovascular Surgery, Sir Ganga Ram Hospital, New Delhi 110060, India

References

1 Sharma BK, Sagar S, Chugh KS, Sakhuja V, Rajachandran A, Malik N. Spectrum of renovascular hypertension in the young in North India: a hospital based study on occurrence and clinical features. *Angiology* 1985;**36**:370–378.
2 Chug KS, Jain S, Sakhiya V, Malik N, Gupta A, Gupta A *et al*. Renovascular hypertension due to Takayasu's arteritis among Indian patients. *QJM* 1992;**85**:833–843.
3 Sen PK, Kinare SG, Kulkarni TP, Parulkar GB. Stenosing aortitis of unknown etiology. *Surgery* 1962;**51**:317–325.
4 Kothari SS. Etiopathogenesis of Takayasu's Arteritis and BCG vaccination: the missing link? *Med Hypotheses* 1995;**45**:227–230.
5 Kinare SG, Gandhi MS, Deshpande J. Non-specific Aortoarteritis (Takayasu's disease). Pathology and Radiology. Mumbai: Quest Publications; 1998:17–66.
6 Takeuchi Y, Matsuki K, Saito Y, Sugimoto T, Juji T. HLA-D region genomic polymorphism associated with Takayasu's arteritis. *Angiology* 1990;**41**(6):421–426.
7 Khraishi MM, Gladman DD, Dagenais P, Fam AG, Keystone EC. HLA antigens in North American Patients with Takayasu arteritis. *Arthiritis Rheum* 1992;**35**(5):573–575.
8 Numano F, Isohisa I, Maezawa H, Juji T. HLA antigen in Takayasu's disease. *Am Heart J* 1979;**98**:153–159.
9 Rose S, Mehra NK, Kumar R, Vaidya MC. HLA B5 and B21 antigens in aortoarteritis. *Indian J Pediatr* 1991;**58**:85–89.
10 Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis for Takayasu's arteriopathy. *J Am Coll Cardiol* 1988;**12**:964–972.
11 Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM *et al*. The American College of Rheumatology 1990 criteria for the classification of Takayasu's arteritis. *Arthritis Rheum* 1990;**33**:1129–1134.
12 Sharma BK, Siveski-Iliskovic N, Singal PK. Takayasu arteritis may be underdiagnosed in North America. *Can I Cardiol* 1995;**11**:311–316.
13 Hoffman GS. Takayasu arteritis: lessons from the American National Institutes of Health experience. *Int J Cardiol* 1996;**54**: S99–S102.
14 Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol* 1996;**54**:S141–S147.
15 Park JH, Chung JW, Im JG, Kim SK, Park YB, Han MC. Takayasu arteritis: evaluation of mural changes in the aorta and pulmonary artery with CT angiography. *Radiology* 1995;**196**:89–93.
16 Ueda H, Morooka S, Ito I, Yamaguchi H, Takeda T, Saito Y. Clinical observation of 52 cases of aortitis syndrome. *Jpn Heart J* 1969; **10**:277–288.
17 Lupi HE, Seoune M. Takayasu's arteritis (non-specific aortartritis). In: Lande A, Berkman YM, McAllester Jr HA, eds. *Aortitis: clinical pathological and radiographic aspects*. New York: Raven Press; 1986:173–191.
18 Park JH. Conventional and CT angiographic diagnosis of Takayasu arteritis. *Int J Cardiol* 1996;**54**:S165–S171.
19 Muranjan MN, Bavdekar SB, More V, Deshmukh H, Tripathi M, Vaswani R. Study of Takayasu's Arteritis in Children: Clinical profile and management. *J Postgrad Med* 2000;**46**:3–8.

*Corresponding author.
E-mail address: rparakh1@yahoo.co.in (R. Parakh).

20 Kumar S, Mandalam KR, Rao VR, Subramanyan R, Gupta AK, Joseph S *et al*. Percutaneous angioplasty in non-specific aorto arteritis (Takayasu's disease): experience of 16 cases. *Cardiovasc Interv Radiol* 1989;**12**:321–325.
21 Sen PK. Non specific aorto/arteritis a monograph based on a study of 101 cases. Bombay: Tata McGraw Hill; 1972.
22 Chhetri MK, Raychaudhuri B, Neelakantan C, Basu J, Chaki S, Saha AK. A profile of non-specific arteritis as observed in Eastern India. *J Assoc Phys Ind* 1974;**22**:839–847.
23 Sharma BK, Jain S. A possible role of sex in determining distribution of lesions in Takayasu Arteritis. *Int J Cardiol* 1998; **66**(Suppl. 1):S81–S84.
24 Sharma BK, Sagar S, Singh AP, Suri S. Takayasu's arteritis in India. *Heart Vessels* 1992;**7**:S37–S43.
25 Subramanyan R, Joy J, Balakrishnan KG. Natural history of aortoarteritis (Takayasu's disease). *Circulation* 1989;**80**: 429–437.
26 Kumar A, Dubey D, Bansal P, Sanjeevan KV, Gulati S, Jain S *et al*. Surgical and radiological management of renovascular hypertension in a developing country. *J Urology* 2003;**170**:727–730.
27 Talwar KK, Chopra P, Narula J, Shrivastava S, Singh SK, Sharma S *et al*. Myocardium involvement and its response to immunosuppressive therapy in non-specific aorto aotiritis (Takayasu's disease) - study by endomyocardial biopsy. *Int J Cardiol* 1988;**21**:323–334.
28 Kasuya K, Hashimoto Y, Numano F. Left ventricular dysfunction and HLA BW 52 antigen in Takayasu arteritis. *Heart Vessel* 1992; **7**:S116–S119.
29 Ishikawa K. Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). *Circulation* 1978;**57**(1): 27–35.
30 Dhingra R, Talwar KK, Chopra P, Kumar R. An Enzyme linked immunosorbent assay for detection of anti-aorta antibodies in Takayasu arteritis patients. *Int J Cardiol* 1993;**40**:237–242.
31 Sima D, Thiele B, Turowski A, Wilke K, Hiepe F, Volk D *et al*. Anti-endothelial antibodies in Takayasu arteritis. *Arthritis Rheum* 1994;**37**(3):441–443.
32 Misra R, Aggarwal A, Chag M, Sinha N, Shrivastava S. Raised anticardiolipin antibodies in Takayasu's arteritis. *Lancet* 1994; **343**:1644–1645.
33 Jain S, Kumari S, Ganguly NK, Sharma BK. Current status of Takayasu arteritis in India. *Int J Cardiol* 1996;**54**:S111–S116.
34 Uppal SS, Verma S. Analysis of the clinical profile, autoimmune phenomena and T cell subsets (CD4 and CD8) in Takayasu's arteritis: a hospital-based study. *Clin Exp Rheumatol* 2003;**21** (6 Suppl. 32):S112–S116.
35 Khalilullah M, Tyagi S. Percutaneous transluminal angioplasty in Takayasu arteritis. *Heart vessel* 1992;**7**:S146–S153.
36 Sharma S, Rajani M, Kaul U, Talwar KK, Dev V, Shrivastava S. Initial experience with percutaneous transluminal angioplasty in the management of Takayasu's arteritis. *Br J Radiol* 1990;**63**:517–522.
37 Tyagi S, Kaul UA, Satsangi DK, Arora R. Percutaneous transluminal angioplasty for renovascular hypertension in children: initial and long-term results. *Pediatrics* 1997;**99**:44–49.
38 Sharma S, Thatai D, Saxena A, Kothari SS, Guleria S, Rajani M. Renovascular hypertension resulting from non-specific aorto arteritis in children: mid term results of percutaneous transluminal renal angioplasty and predictors of re-stenosis. *Am J Roentgenol* 1996;**166**:157–162.

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