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. 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 Khaishi 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
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

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<th>Table 1. Modified diagnosis criteria for Takayasu arteries12</th>
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<tr>
<td><strong>Three major criteria</strong></td>
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<tr>
<td>Right mid subclavian artery lesion</td>
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<td>Characteristic signs and symptoms of at least one-month duration.</td>
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<td>The minor criteria</td>
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<td>High ESR</td>
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<td>Carotid artery tenderness</td>
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<td>Hypertension</td>
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<td>Aortic regurgitation or Annulo-aortic ectasia</td>
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<td>Pulmonary artery lesion</td>
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<td>Left mid common carotid lesion</td>
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<tr>
<td>Distal brachiocephalic trunk lesion</td>
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<td>Descending thoracic aorta lesion</td>
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<td>Abdominal aorta lesion</td>
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<tr>
<td>Coronary artery lesion</td>
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<td>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.</td>
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<td>Persistent blood pressure in brachial &gt;149 mmHg, or popliteal &gt;160/90 mmHg by auscultation or Doppler echocardiography or angiography.</td>
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<td>By angiography or two-dimensional echocardiography.</td>
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<td>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.</td>
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<tr>
<td>Abrupt narrowing, dilatation or aneurysm, luminal irregularity or any combination determined by angiography: tortuosity alone is unacceptable.</td>
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<tr>
<td>Narrowing, dilatation or aneurysm, luminal irregularity or any combination determined by angiography: tortuosity alone is unacceptable.</td>
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<td>Documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus.</td>
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<th>Table 2. Sensitivity and specificity for the various diagnostic criteria14</th>
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<td>Criteria</td>
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<td>Ishikawa</td>
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<td>American College of Rheumatology</td>
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<td>Sharma et al.</td>
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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.

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. 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%). Kasuya et al. have reported that patients with TA and HLA Bw52 antigen have a more severe left ventricular involvement. 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.

Dhingra et al. had detected anti-aortic antibodies in patients with TA. Sima et al. demonstrated anti-endothelial antibodies by enzyme linked immunosorbent assay. Misra et al. have reported elevated titers of IgG anticardiolipin antibodies in 14 of 34 patients of TA. They had also documented an elevated CD4+ subset of T lymphocytes in patients with TA. An expansion of CD4+:CD8+ ratio, a high basal protein kinase activity and a high intracellular calcium concentration has been observed. 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 T cell 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.

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.

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. The clinical benefit of renal angioplasty was seen in 85% of TA cases. However, re-stenosis occurred in 24.23% cases at a median follow up of 4.6 years. 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. 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 under standing of disease aetiology and pathogenesis is required for better outcomes in the future.

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