Takayasu arteritis (TA), (also known as pulseless disease, non specific aorto-arteritis, aortic arch syndrome or middle aortic syndrome), is a chronic inflammatory disease of unknown etiology that involves the aorta and its major branches, leading to arterial stenosis or occlusions with subsequent cerebral, renal, limb, mesenteric or cardiopulmonary ischemia (1, 2).

TA has a world wide distribution. The majority of reports, however, have come from Japan, India, China, Sri Lanka, Singapore and a few reports from North America, Europe and South Africa.

Etiopathogenesis

A number of factors like connective tissue disorders, infections, genetic factors and immunological phenomenon have been implicated in the etiology of TA. However, the issue remains far from settled.

Infections

A variety of infectious agents have been implicated in the etiology of TA viz. streptococcus and mycobacterium tuberculosis. Evidence of infection with tuberculosis has been reported on the basis of presence of co-existent tubercular lesion in lungs and para-aortic lymph nodes as well as report of presence of Langhans giant cells in lesions of TA. It is important to note that in Japan where disease is widespread, tuberculosis has become almost extinct. Recent reports, however, have found no evidence of tuberculosis as an etiologic factor (3). It has been hypothesized that TA may be related to abnormal immune response to BCG vaccination (4).

Connective tissue disorders

There are several reports of association between TA and connective tissue disorders like rheumatoid arthritis, SLE, sarcoidosis, ulcerative colitis and Crohn's disease. However, any definite proof of causal association between connective tissue disorders and TA is lacking.

Genetic factors

A number of reports of occurrence of the disease in monozygotic twins and in sibs, point towards a possible genetic predisposition in this disease. Several HLA antigens have been found to be associated with this disease — A9, A10, B5, BW52, DW12, DH0 and MT1. It has been observed that patients with HLA BW52, DW12 and MT1 suffer from more severe disease.

Immunity

The possibility of an immune mediated etiology has been supported by findings of high gamma globulins, circulating immune complexes, presence of aortic antibodies and failure to detect an etiologic agent in walls of vessels affected by the disease. Dhar et. al. (5) demonstrated an increase in ratio of CD4+: CD8+ cells,
basal protein kinase C activity and a high intracellular calcium in T-lymphocytes. The exact stimulus triggering the T-cells and the molecular mechanisms underlying the immunological dysfunction are not known.

Dense NK cell infiltration has been shown in wall of aorta and it has been proposed that they cause vascular injury by releasing a cytolytic factor called 'Perforin'.

Recently, Gulati et al. demonstrated that endothelial cells in patients with TA may induce an inhibitory effect on lymphocytes (6). They have suggested that membrane antigens on the endothelial cells may not be expressed sufficiently to activate the immune response in these patients. This study points to the possible role of endothelial cells in causing injury to the blood vessels.

**Classification of TA**

Definite diagnosis of TA is made on the basis of typical angiographic findings. Most commonly used angiographic classification of TA was given by Ueno et al. (7), who divided the disease in three categories based on the angiographic extent of involvement of disease. This classification suffered the drawback of not taking into account coronary or pulmonary vascular involvement and not stratifying the disease according to involvement of isolated ascending, descending thoracic or abdominal aorta. To resolve above fallacies, a new classification was devised in 1994.

**Classification of Takayasu Arteritis (8)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Type I</td>
<td>Primarily involves the branches from the aortic arch.</td>
</tr>
<tr>
<td>Type IIa</td>
<td>Involves ascending aorta, aortic arch and its branches.</td>
</tr>
<tr>
<td>Type IIb</td>
<td>Involves the ascending aorta, aortic arch, its branches and thoracic descending aorta.</td>
</tr>
<tr>
<td>Type III</td>
<td>Involves descending thoracic abdominal aorta and or renal arteries.</td>
</tr>
<tr>
<td>Type IV</td>
<td>Affects mainly the abdominal aorta and or renal arteries.</td>
</tr>
<tr>
<td>Type V</td>
<td>Combines features of both types IIb and IV. Moreover involvement of coronary and pulmonary arteries is designated as C+ and P respectively.</td>
</tr>
</tbody>
</table>

**Diagnostic Criterion**

Clinical diagnosis of TA poses a difficult challenge to clinicians due to lack of pathognomic features of this disease. Various diagnostic criteria have been formulated to clinically diagnose TA.

**Ishikawa's Criterion (9)**

In 1988, Ishikawa proposed a set of criterion to distinguish TA from atherosclerosis. The criterion had a sensitivity of 84% in his 96 patients with TA.

**Criterion**

The proposed criteria consists of one obligatory criterion, two major criteria, and nine minor criteria.

Obligatory criterion of Age < 40 yrs.

Two major criteria are left mid subclavian artery lesion, right mid subclavian artery lesion.

Minor criteria are high ESR, carotid artery tenderness, hypertension, aortic regurgitation or annuloaortic ectasia, pulmonary artery lesion, left mid common carotid lesion, distal brachiocephalic lesion, descending thoracic aorta lesion, descending abdominal aorta lesion.

In addition to the obligatory criterion, presence of two major criteria, or one major and two or more minor criteria, or four or more minor criteria suggest a high probability of the presence of Takayasu's disease.
There are, however, a number of pitfalls of this criterion:

(i) It does not take into account the geographic and racial variations of this disease.

(ii) Obligatory criterion of age < 40 years: Even in Japan almost 15.1% of patients with TA had age of onset more than 40 years (second nationwide survey). Reports from several other parts of world including India, document age onset more than 40 years in patients of TA (3).

(iii) It places emphasis on the presence of active characteristic signs and symptoms of 1 month duration prior to age of 40 years. Presence of these is helpful in diagnosis but have been regarded as minor criterion.

(iv) Ishikawa defined abdominal aortic lesion as narrowing, dilatation or aneurysm, luminal irregularity, or any combination and absence of lesion in aorto-iliac region consisting of two cms of terminal aorta and bilateral common iliac arteries. However, involvement of iliac arteries has been reported to occur in 11-29% patients with TA (3).

Modified Diagnostic Criterion for TA

Recently Sharma et. al. have proposed modification to Ishikawa’s criterion for the diagnosis of TA (10). The proposed modification include: (a) removal of the obligatory criterion of age less than 40 years, (b) inclusion of characteristic signs and symptoms as a major criterion, (c) removal of age in defining abdominal aortic lesion, and (c) an addition of coronary artery lesion in absence of risk factors. Presence of two major or one major and two minor criterion or four minor criterion suggests a high probability of TA. When applied to 16 Indian patients of angiographically proven TA and 20 control subjects, it had a sensitivity of 92.5% and specificity of 95%, that was higher than that of Ishikawa’s criterion, sensitivity 60.4% specificity 95% (9). Similarly, this criterion had a 96% sensitivity and 96% specificity in 79 Japanese patients of TA and 79 control subjects. Adoption of these criterion is expected to prevent the possibility of an under diagnosis of TA (11).

Management of TA

The management of TA includes medical therapy during the acute phase and surgical or catheter based revascularisation procedure during chronic stenotic phase of disease.

Medical Therapy

Medical therapy remains the mainstay of therapy in active phase of disease. Corticosteroids (prednisolone 0.5mg/kg - 1mg/kg) have been shown to bring out dramatic improvement in systemic inflammatory symptoms within days to weeks. Ishikawa (12) reported a series of 118 cases followed up for 11 ± 7 years. Of the 78 cases requiring steroids, therapy could be stopped in 20 cases, 38 continued to be on maintenance therapy and 19 received interrupted therapy. Eight of 9 cases, who received continuous therapy with steroids, showed angio graphic evidence of regression of disease whereas, of the 5 cases who received interrupted therapy, 3 showed evidence of disease progression.

In the series of Kerr et. al. (13) remission was achieved in 52% cases in first course of therapy and 60% cases atleast once. The estimated median time to remission was 33 months in adults and 11 months in children. In 25 cases, cytotoxic agents were added because of failure
to induce remission with steroids alone, or inability to taper steroids once the disease was controlled. 40% of these cases attained remission at least once. Median time to remission was 20 months. Twenty-three percent patients never attained any remission. Hoffman et al. (14) reported 81% of steroid resistant or relapsing TA achieving remission with combination therapy of glucocorticoids and weekly low dose methotrexate (MTX).

Cyclophosphamide and azathioprine have also been tried in a small group of steroid resistant cases with favourable results (15). However, further long-term studies are required for establishing a definite role of immunosuppressive agents.

Other drugs used include antihypertensives. A combination of drugs is usually needed.

To summarize, corticosteroids have been shown to induce remission in significant number of cases with active disease. MTX, cyclophosphamide and azathioprine may induce remission, or help in reducing doses of steroids in steroid resistant or frequently relapsing patients.

Revascularization Procedures

In chronic stage, the management of TA is based on revascularisation of the involved organs either by surgery or by balloon angioplasty.

(A) Subclavian angioplasty and stenting

Subclavian arteries are amongst the most commonly involved vessels in TA. Surgical revascularisation involving bypass of the steno occlusive lesions was considered as the treatment of choice in the past. It involved a high mortality (5-8%) and complication rates as high as 23%, comprising of chylothorax, endarterectomy thrombosis, pneumothorax, pleural effusion, neck lymph fistula, phrenic nerve palsy and Horner's syndrome (16).

Joseph et. al. (17) described Percutaneous Transluminal Balloon Angioplasty (PTBA) of subclavian artery in 24 patients of TA. The lesions were focal (<3 cm) in 14 arteries and diffuse in 12 arteries. Initial success was achieved in 81% cases (17 of 19 stenosis and 4 of occlusions). On follow up, restenosis occurred in 8 arteries, all of which had extensive lesions. The cumulative patencies for short and long segment disease were 100% and 50% respectively.

Tyagi et. al. (18) reported their 10 year follow up experience with 35 cases of TA. High inflation pressure were required for dilation of these lesions (9.9 ± 4.6 atm). The procedure was successful in 88.8% cases with subclavian artery stenosis and 50% cases with short segment chronic total occlusion. Restenosis occurred in 20.8% cases over a follow up of 43.4 ± 24.1 months. Most of these patients had diffuse long segment disease, chronic total occlusion, or evidence of disease activity.

PTBA of diffuse long segment disease and chronic total occlusion has frequently met with suboptimal results, high rates of reocclusion and prohibitive incidence of restenosis. We have performed de novo stenting of 4 subclavian arteries. Three patients had total chronic ostial occlusion and one patient had long segment diffuse disease with extensive collaterals. These cases were given J&J stents (Palmaz P 204 in 2 cases and Palmaz P 304 in 1 case) and one case was given AVE iliac bridge stent. There was 100% primary and secondary patency (19). We recommend that in patients with suboptimal results after PTBA, or flow limiting dissection, stenting is useful. In patients with diffuse long
Aortoplasty & Stenting

The surgical management of aortic stenosis involved the bypass of stenosed segment of aorta and was associated with high mortality rates, problems of graft occlusion and anastomotic site aneurysms. Besides, progressive inflammatory nature of disease has precluded widespread use of reconstructive surgery (20).

PTBA offers a new simple, cost effective and safe method for relief of stenotic lesions. Rao et al. (21) reported cumulative patency rate of 67% in a 52 month follow up (mean 86 weeks) of 16 cases undergoing PTBA of aorta. Complications related to the procedure occurred in 5 (31.2%) cases.

Tyagi et al. (22) described their experience with PTBA of 38 cases of TA involving aorta. Balloon dilatation was successful in 34 cases and resulted in the reduction of mean peak systolic pressure gradient (PSG) from 75.2 ± 29.1 mmHg to 24.8 ± 19 mmHg (p<0.001). Hemodynamic and angiographic follow up study was performed in 20 cases. In 7 patients, gradient further decreased to less than 15 mmHg; did not change in 12 and increased in one case.

A reappraisal of this study indicates that in 11 patients after PTBA, gradient continued to be higher than 20 mmHg and in 4 more than 40 mmHg. The resting gradient is further likely to increase on exercise. In the present era, this persistence of gradient is probably unacceptable. We propose that successful aortoplasty should have a residual gradient of less than 20 mmHg. We have performed stenting of aorta in 4 cases (23). Three patients had long segment stenosis and 1 case had short segment stenosis. Five wall stents were used in four cases. Procedure was successful in all cases and the PSG completely disappeared in all cases. Angiographic follow up at six months is available in 3 (75%) cases. Benefit has been persisting and there is no restenosis. In one case, a small aneurysm has formed at the lower end of stent. Sharma et al. (24) and Behl et al. (25) have reported successful use of self expanding wall stents in descending thoracic aorta and abdominal aorta respectively for dissection following PTBA. Tyagi et al. (26) reported use of J & J stent for recurrent long stenosis due to TA in a child.

We propose that patients who have long segment disease, or who have dissection or presistance of gradient more than 20 mmHg after PTBA (suboptimal results) should undergo aortic stenting.

Renal angioplasty and stenting

TA is the commonest cause of renovascular hypertension in Asian countries (27). Renal lesions in TA are often bilateral and involve the ostia. The management of renovascular hypertension usually requires polydrug therapy leading to side effects and poor patient compliance.

Surgical revascularisation involves use of aorto renal bypass grafts (saphenous vein or PTFE), direct aortic remiplantation or thrombo endarterectomy. This procedure is made difficult because of extensive perivascular fibrosis and diffuse multifocal disease. Some patients with non-functioning kidney may require nephrectomy due to uncontrolled hypertension. In contrast, PTBA of renal arteries has shown excellent immediate and long term results.

Dong et al. (28) reported their experience with 22 patients followed for atleast 6 months. Normalization of blood pressure was achieved in 13 and improvement in 6 patients giving an overall success rate of 86%.
Tyagi et al. (29) performed renal angioplasty in 54 patients. Restenosis occurred in 13.5% cases with a success rate of 89.3%. In another study by the same author on PTBA of renal arteries in 35 children (age 5-14 years), the procedure was successful in 88.6% but restenosis occurred in 25.8% (8 cases) of TA (30). The higher restenosis rate in children was probably because of small diameter of renal vessels, and active phase of disease. The authors have a case with bilateral renal artery stenosis who underwent PTBA of both arteries with good initial results but developed restenosis in only one renal artery despite presence of activity of disease. They observed that although disease activity increase the chances of restenosis, not all vessels restenose with disease activity and some vessels may become completely occluded so as to preclude any further procedure. Therefore, in case of severe uncontrolled renovascular hypertension, the procedure should be carried out despite evidence of disease activity so as to prevent progressive renal damage as a consequence of hypertension.

We have performed renal stenting in two cases with TA. In one 11 year old child, AVE Micro I stent was used for flow limiting dissection after PTBA. Second patient had severe ostial stenosis with suboptimal results of PTBA. Both the patients are doing fine on follow up. We propose that patients with suboptimal results or flow limiting dissection after PTBA and patients with diffuse or ostial disease of renal artery should undergo stenting. Both self expanding (Wall stent, Symphony) and balloon mounted stents (J & J stent, AVE, Saint Come) can be safely used.

(D) Carotid angioplasty and stenting

The experience in carotid angioplasty is limited to occasional case reports in literature. Hogins et al. (31) first described carotid angioplasty in literature in 19... Murakami et al. (32) described persistent benefit angioplasty over 10 year follow up period for carotid artery stenosis in one patient who presented with hemiparesis.

Joseph et al. (33) described a successful single case of carotid stent angioplasty via transseptal route because of absent pulses in all four limbs.

We have attempted carotid angioplasty and stenting in 6 patients (19). Four patients had chronic total occlusion of common carotid and one had spontaneous dissection of left common carotid artery. In one patient with chronic total occlusion of carotid artery, guidewire could not be negotiated across the lesion and the procedure was abandoned. In other 5 patients after predilatation, stents were deployed. Three patients received Wall stents and two patients received J & J stent (P 204). No residual stenosis was seen in any case. In patients with active disease developed stent restenosis. In one of them, repeat high pressure dilatation gave acceptable results.

Our experience indicates that carotid angioplasty and stenting is safe and effective in management of stenosis lesion of carotid arteries. Stenting should preferably be avoided in acute phase. However, not all lesions due to disease activity restenose and if the symptoms persist are likely to cause irreversible damage, PTBA and stenting should be performed despite disease activity.

(E) Coronary angioplasty and stenting

The results of CABG (Coronary Artery Bypass Graft) in TA are not satisfactory. It is difficult to construct proximal anastomosis of the grafts because of extremely thickened aortic wall which may contribute to the late proximal occlusion of bypass grafts.
There are several case reports describing excellent immediate and long term results of angioplasty with or without stenting of coronary arteries (34).

(F) Mesentric angioplasty and stenting

The patients are usually asymptomatic but occasionally may present with ischemic bowel syndrome. Ozdil et al. (35) described a case who underwent successful angioplasty and stenting of superior mesentric (Palmaz P 204) and coeliac trunks (Palmaz P 154 stent).

Tyagi et al. (36) similarly described marked improvement in symptomatic status of a patient presenting with chronic mesentric ischemia after stent angioplasty.

Conclusions

TA is a chronic inflammatory disease involving the aorta and its major branches causing significant morbidity. The etiology of TA is not clearly elucidated so far. Bulk of evidence, however, is in favour of an immune abnormality as the primary causative factor. Steroids with or without immunosuppressive therapy remain the mainstay of therapy during the active stage of disease. PTBA with or without stenting has emerged as the treatment of choice for management of stenotic lesions of TA. Occasional in-stent restenosis and recurrence of disease at new sites however remain potential problems.

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References


