Current Status of Aortoarteritis in India

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Takayasu’s arteritis (TA) is an inflammatory vascular disease of the young involving the large elastic arteries resulting in occlusive or ecstatic changes mainly in the aorta and its major branches as well as the pulmonary artery and its branches. Non-specific aortoarteritis was introduced to the medical fraternity in 1827 by R. Adams who was the first physician to note absence of pulse in all four extremities. In 1856 Savory reported a case of young female with absence of pulses. In 1908, Mikito Takayasu, a Japanese ophthalmologist described a peculiar wreath-like appearance of retinal blood vessels with absence of radial pulse. According to ICD-9 classification of diseases, NSAA is classified at 446.7.

Non-specific aortoarteritis is predominantly a disease of young females in their second and third decades. It occurs worldwide and no race seems to be immune. Age of onset may range from infancy to late middle age. Sharma et al have shown that childhood onset of NSAA is not rare and Kerr et al had 1/3rd of his cases comprising of childhood onset of NSAA. Waern et al however found a higher mean age of onset (41 yrs.) in a European study. In Japan, mean age at presentation is quoted to be around 29 years. The disease has a predilection for females with wide geographical variations. In Japan it is 8:1, in Mexico 5:1, in India 4:1 and in Israel 1.2:1. In a recent series by Panja et al M:F ratio was 1:6.4.

There is also geographical variation in the clinical presentations of NSAA vis-à-vis pattern of vascular involvement by the disease. In Japan, predominantly proximal aortic involvement with features of “reversed coarctation” is seen. In Southeast Asia and Africa, descending thoracic and abdominal aorta involvement with renovascular lesions, the so called “middle aortic syndrome” is found more commonly. In North Europeans, frequent association with rheumatic, rheumatoid (Rush et al) arthritis and systemic lupus (Saxe et al) are seen. There is patchy aortic involvement with occasional involvement of aortic valves.

Concurrent geographical variation in genetic predisposition is also marked so far as HLA-association is concerned. In Japan high association with HLADR2, MB1, BW52, DW12, DQW1 (Dong et al) and among North Indian patients the incidence of various types as Type-I - 22%, Type-II - 25%, Type-III - 53% and Type-IV - 26%. Our study involving 650 patients belonging to Eastern India and Bangladesh (largest series from India) revealed somewhat contrasting data - Type-I - 16%; Type-II - 8%; Type-III - 76%; Type-IV - 36% and Type-V - 10%.

Aortoarteritis is a panarteritis involving all the three layers causing extensive intimal proliferation, inflammation of media and adventitia followed by marked fibrous scarring. Histologically there is round cell infiltration, cuffing of vasa vasorum and destruction of tunica media leading ultimately to gross fibrosis. In older cases, hyalinization of deeper layers of intima and dystrophic calcification can be seen. The appearance of aortic intima is closely related to the activity and duration of the disease. Circumferential intimal thickening, plaques and patches of raised intima are frequently seen on the inner surface of the aorta. In advanced cicatricial stage, the aortic intima may have ‘tree-back’ appearance similar to that of luetic aortitis. Skipped areas of aortic involvement are quite characteristic of aortoarteritis.

In the majority of cases, this disease is insidious in onset. However sudden onset is not very rare. Ishikawa reported insidious onset of symptomatology in 76% and sudden onset in 24%. Disease course is not uniform. In about 40% of cases the symptoms may follow plateau-crescendo course. In 36% of cases it is plateau, in 19% of cases it is decrescendo and in about 5% it follows a decrescendo-plateau-crescendo pattern.
In the late chronic phase symptoms are due to the obliterative and inflammatory changes in blood vessels. Patients present with diminished or absent pulse (96%), bruits (94%), hypertension (72%), heart failure (28%), abnormal fundi secondary to hypertension (41%). In addition patients may present with dyspnea on exertion, palpitation, intermittent claudication or angina pectoris. Neurologic symptoms include headache, syncope, hemiplegia and visual disturbances.

In this context, our study of 650 cases revealed inequal pulse (96%), hypertension (72%), oliguria due to renal failure (30%), intermittent claudication (25%). CNS symptoms (amaurosis fugax, syncope, TIA - 22.5%, eye changes (8.1%) and skin manifestations (erythema nodosum, Raynaud’s phenomenon, leg ulcers - 3.8%).

Incidences of the various clinical features in children do not differ much from those of adults and in our series we observed congestive cardiac failure in 76%, hypertension in 70.5%, dilated cardiomyopathy in 20% and involvement of the thoracic aorta in 58.8% of cases.

Commonest aetiology for systemic hypertension is renal artery stenosis. Other causes are - atypical coarctation, reduced aortic capacitance as well as diminished baroreceptor reactivity.

Heart failure in NSAA is related to systemic hypertension or valvular regurgitant lesion. Isolated cardiomyopathy may be the underlying cause in about 5% of cases. Aortic regurgitation has been reported in 7.24%. Mitral regurgitation has been reported in 11.4%. Aortic dilatation with separation of the cusps is the predominant cause of aortic regurgitation, however, thickening and puckering of aortic valve leaflets and thickening in the left atrial endocardiaum was also reported by Chhetri et al. Incidence of aneurysms in aortoarteritis varies from 2-26.7%. Aneurysmal form of aortoarteritis is associated with a higher incidence of aortic regurgitation, hypertension and elevated ESR as compared to the non-aneurysmal form.

Study reports from Japan and Mexico revealed incidence of pulmonary artery involvement to be between 44% and 100%. This is much lower among Indians. Tyagi et al in their study with North Indian patients reported this incidence as 26.3%. Our study came to conclusion that Eastern India and Bangladesh revealed an incidence 36% of pulmonary arterial involvement. Both stenotic and occlusive lesions are seen in right and left upper lobe artery is most frequently involved. There is no relation between systemic and pulmonary arterial systems as regards the extent and activity of the involvement.

Pulmonary hypertension in aortoarteritis can be due to three factors: pulmonary arterial involvement; left ventricular failure; combined pulmonary arterial and left ventricular origin. Coronary artery involvement is mostly limited to coronary ostium and proximal coronary arteries but diffuse and triple vessel disease is also noted. Naturally patients may suffer from angina pectoris, acute myocardial infarction, congestive cardiac failure and even sudden cardiac death (SCD).

Chronic reduction of the orbital and ocular blood flow produces hypoxic retinal vascular changes which has been classified into four stages by Uyama and Asayma. Stage - 1, retinal veins become distended; Stage - 2, Microaneurysm formation - occurs at systolic retinal arterial pressure of 30 mmHg; Stage -3, Arterio-venous anastomosis; Stage - 4, ocular complications - e.g. cataract, ruberosis, retinal ischaemia, neovascularization, proliferative retinopathy and vitreous haemorrhage.

Clinical diagnosis of aortoarteritis is based on proposed diagnostic criteria by Ishikawa (1988). These consist of one obligatory criterion (age <40 years at diagnosis or onset of disease), two major criteria (left and right mid subclavian artery lesions) and nine minor criteria (high ESR, common carotid artery tenderness, hypertension, aortic regurgitation or anulo-aortic ecatisa, lesions of pulmonary artery, left mid common carotid artery, distal branchio-cephalic trunk, thoracic aorta and abdominal aorta). 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 the presence of aortoarteritis. These criteria have greater sensitivity for patients with active disease than for those with inactive disease. Geographic variation in pattern of arterial involvement may reduce sensitivity of these criteria.

Recently American College of Rheumatology (1990) has selected ‘6’ criteria for diagnosis of aortoarteritis. These include age of onset of disease <40 years; claudication of extremities, decreased brachial artery pulse; BP difference >10 mmHg between arms; bruit over subclavian arteries or aorta and arteriogram abnormality. Presence of at least ‘three’ of these ‘six’ criteria suggests the diagnosis of aortoarteritis, which have a sensitivity of 90.5% and a specificity of 97.8%.

Specific treatment of the disease is not available in the absence of our knowledge of its exact aetiology. Treatment is mainly based on the clinical symptomatology and the possible immunologic basis of the disease. Medical therapy is recommended to patients with active disease, in whom surgery and balloon angioplasty are not feasible and in patients who refuse to undergo balloon angioplasty or surgery.

Glucocorticoids in high doses (prednisone, 1 mg/kg body weight per day) are well established as primary therapy of Takayasu arteries and often dramatically improve the constitutional symptoms, halt disease progression in patients in the systemic inflammatory stage and lower the erythrocyte sedimentation rate (ESR) toward normal. Prednisone is tapered to an alternate day regimen after three months of daily therapy. Unlike giant cell (temporal) arteritis, patients with aortoarteritis may require treatment with low dose cortico steroid for extended periods of time. If prednisone can not be tapered to an alternate day regimen after three months or if there is progression of disease on steroid therapy, cytotoxic drugs like cyclophosphamide (2 mg/kg/day) or azathioprin (100 mg/day) has been used in some studies with fair results.
Alternatively low dose methotrexate (0.3 mg/kg/week) may enhance the efficacy of steroid therapy and facilitate steroid tapering. Clinical and haemodynamic improvement have been reported in patients with myocarditis associated with aortoarteritis following immunosuppressive therapy.

Methotrexate and dapsone appear to be useful steroid sparing agents and newer biological, immunomodulatory agents may also become useful in clinical management.

Antihypertensive and decongestive therapy are given to patients with heart failure and systemic hypertension, usually with good response. Renovascular hypertension responds poorly to drug therapy.

Efficacy of oral anticoagulants, antiplatelet agents and vasodilators for treatment of aortoarteritis is not established. Sen et al instituted empirical antitubercular treatment demonstrating tubercular lesions, positive Mantoux's test and increased erythrocyte sedimentation rate. But at present there is no role of empirical antitubercular treatment.

Spontaneous regression with steroid was noted in four cases in our series.

Major advancement in the treatment of this otherwise morbid condition has been brought by percutaneous transluminal angioplasty of stenotic vascular lesions. Lesions in Takayasu arteritis are purely stenotic in 85% of patients, purely dilatative in 2% and mixed in 13%. Stenotic lesions in aorta and its branches have been dilated with excellent immediate and long term follow up results.

We have performed balloon angioplasty of aorta in 52 patients (58 lesions) since 1978, using 7-20 mm. Balloon inflated at 4-17 atmospheric pressure. Deployment of stent was done in 12 dilated lesions. Of the 58 lesions, 28 lesions were in the thoracic aorta and 30 lesions in the abdominal aorta. The mean diameter of stenosed segment increased from 5.1 ± 2.7 mm to 10.6 ± 5.2 mm with decrease in mean peak systolic pressure gradient from 68.8 ± 21.6 mmHg to 28.4 ± 19.6 mmHg. On follow up of 1-5 years, restenosis was noted in three thoracic aortic lesions (25%) and six abdominal aortic lesions (38%). Restenosis was noted in one stented case (11%). Minor dissection at the local dilated segment was very much frequent but this did not alter outcome. Stenotic lesions in aortoarteritis are often rigid and may require much higher inflation pressure for dilatation which should be done cautiously to avoid rupture of aorta and aneurysm formation. Post-balloon angioplasty aneurysm formation was noted in one case which was successfully treated by implantation of covered stent graft.

Balloon angioplasty of stenosed subclavian arteries was attempted in 64 lesions in 56 patients. Lesions were dilated with HIGH-FIVE peripheral angioplasty balloon. Stent was deployed in 14 lesions. GLIDE GUIDE wire was used for total occlusion. Primary success rate was 80% (48 lesions). Stenosed segment less than 10 cms (40 lesions) have had higher success rate (90% - 36 lesions) than stenosed segment more than 10 cms (20 lesions - 60% success rate). Restenosis was noted in six lesions (12.5%) on 1-3 years follow up. Minor complication was noted only in one case.

Balloon angioplasty of iliac and sapheno-femoral systems were also highly successful and use of GLIDE guide wire resulted in high success rate in crossing the lesions. Lesion length is a very much determining factor in success as in all 20 lesions (18%). Redilatation was attempted in all 20 lesions and were successfully redilated. Restenosis was noted in six stented lesions (2.76%). There was marked symptomatic improvement and decrease in blood pressure in hypertensive patients (Figs. 1 and 2).

Balloon angioplasty of carotid arteries was attempted in 40 lesions in 36 patients with 70% (28 lesions) success rate. All the lesions were predilated with coronary angioplasty balloon (OMNIPASS - 2.5 mm-3.5 mm). Self expanding wall stent was deployed successfully in four lesions. Major embolic event was noted in one case and transient neurologic deficit in three cases. On follow up restenosis was noted in seven cases and stent deformation in one case.

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Overall efficacy of balloon angioplasty in aortoarteritis was highly encouraging. Hypertension was controlled in 87% and claudication improved in 86%. Marked reduction in five years mortality was also noted - 9% after successful angioplasty, 42% after failed angioplasty and 25.8% in the control group.

The indications of surgery in the treatment of Takayasu arteritis are not well established. Surgery is generally performed to correct renovascular hypertension, relieve cerebral ischaemia, repair aortic or arterial aneurysms, treat aortic regurgitation or by-pass coronary arteries. Surgery during the active phase of the disease carries significant risk of reocclusion and peri-procedural complications. This hold true for percutaneous procedure also.

Various modalities of surgical treatment are a) by pass of the obstructed arteries, b) resection of the narrowed segment and replacement with an interposition graft, c) patch aortoplasty for short segmental lesion, d) endarterectomy, e) excision of sacular aneurysms and f) aortic valve replacement.

The natural history of NSAA has two distinct phases; an active or pre-pulseless phase and a chronic or pulseless phase. Active phase may remit spontaneously in three months or may progress insidiously into the chronic phase. There can be exacerbations of activity during the chronic illness. Not all patients have a manifest acute phase and may present in chronic phase only. In the chronic phase, the inflammation leads to either stenosis or occlusion (85%) of the affected vessel, aneurysm formation (2%) or both (13%). The best documented report on natural history of this disease from India is by Subramanyan et al21 in which they studied 88 patients (54 women and 34 men) for a follow up period of 83.6 ± 74.4 months from the onset and 33.2 ± 37.0 months from the diagnosis. The survival rate at 5 years after diagnosis was 80.3% after which the survival curve flattened out with no further mortality. As with the survival curve, the event-free survival curve also flattened out after the first five years of diagnosis. Ishikawa27 has reported higher rates of survival (89.7%) and event free survival (86.9%) at five years after established diagnosis. Cardiac failure was the single most common cause of death. Improvement in clinical condition, probably spontaneous can occur in young patients. Medical therapy is not much efficacious in altering the long term outcome of the disease. Childhood-onset particularly when associated with a DCM like picture carries an ominous prognosis. Failed angioplasty also implicates high mortality. Early angioplasty of stenosed vessels is a real hope in this otherwise morbid and potentially fatal disease.

Early angioplasty improves survival in all groups of aortoarteritis, but still we have to go a long way for proper claudication of aetiology of this disease, henceforth the treatment and prevention also.

REFERENCES
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3. Savory. W. S. A Case of a young women in whom the main arteries of both upper extremities and of left side of neck were throughout completely obliterated. Med Chir Trans Lond 1856;39:205.

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**Announcement**

*The Program of ICP on 20 January, 2004 (Tuesday) shall be as follows:*

**General Body Meeting ICP :** 13.30 - 14.30 hrs

**Scientific Programme of ICP -** Chairpersons : Dr S.N Shah, Dr Y.P Munjal, Dr S.Kamath : 14:30 to 16:00 hrs
- New concepts in diagnosis and treatment of diseases
- Aspirin Resistance: Current concepts
- Asymptomatic Gall stones: Current strategies
- Management of systematic Rheumatic Diseases
- Designer Insulins

**Convocation of ICP :** 16:00 to 18:00hrs

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*Sd/-
Dr. PC Manoria
Dean Elect ICP*