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Takayasu arteritis in India

B.K. Sharma,[1] S. Sagar,[1] Aminder P. Singh,[1] and S. Suri[2]

[1] Department of Internal Medicine and [2] Radio Diagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh-160012, India

Summary. Takayasu arteritis is the commonest cause of renovascular hypertension in India. The clinical and radiological features, complications and course of 83 patients (51 females, 32 males) seen during the period from 1972–1990 are described in this study. The age of the patients ranged from 5 to 53 years with the mean ±SD of 26.9 ± 9.7. Hypertension (n = 50) and the related symptom of headache (n = 40), dyspnea (n = 24), and giddiness (n = 20) were common at presentation. Twelve patients were in congestive cardiac failure. The symptoms of activitly with fever and arthralgia were present in only 16% contrary to reports from Japan and Mexico. Abnormal arterial pulses and bruit over abdominal (37%) or extra abdominal great arteries (25%) were useful clinical clues to suspect Takayasu arteritis. Rapid sequence intravenous urography was a sensitive screening procedure and predicted correctly the presence of renovascular disease in 80% of the patients. The diagnosis was confirmed on aortography in 72. In the rest, the clinical features and autopsy findings confirmed the same. The four patterns of the disease based on the anatomical extent of involvement were recognised. These were: type I (n = 8) with involvement of aortic arch and its branches, type II (n = 25) descending thoracic and abdominal aorta type III (n = 46) combination of I and II and type IV (n = 4) pulmonary artery in addition to any of the above.

Antihypertensive drug therapy was the mainstay of treatment, but surgery in carefully selected patients was rewarding. Eleven patients died during 6 years after the initial diagnosis mainly due to cardiac, renal and cerebro-vascular complications. The course of the disease seems to be slowly progressive and in many patients becomes static for long periods.

Address correspondence to: B.K. Sharma

Key words: Takayasu Arteritis – Hypertension – Retinopathy – Renal artery stenosis

Introduction

Takayasu arteritis is characterised by involvement of the aorta and its major branches in a chronic, non-specific and usually progressive inflammatory process. This disease is also known as 'non-specific aortoarteritis' as was proposed by Sen [1]. It is more prevalent in Japan, India, China, Korea, Thailand and other South-east Asian countries (C.Y. Hong, personal communication April, 1990.) [2–6]. In India, the disease has been reported from almost all the parts of the country [7–13]. The basic pathological process is a panarteritis that appears to begin with inflammation of the adventitia with subsequent involvement of the media and intima leading to vascular stenosis, occlusion or aneurysm formation. The clinical manifestations are varied and depend upon the development of secondary hypertension, the commonest mode of presentation, and the involvement of the arteries to various organs viz retinopathy; cardiac involvement, cerebrovascular occlusive stroke, renal failure and premature death. While the precise etiology of aortoarteritis remains obscure the natural history is becoming somewhat clearer. This study is an attempt to document the clinical and radiological features, complications and clinical course of patients of Takayasu arteritis at our tertiary care Nehru Hospital attached to the Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Materials and methods

Chandigarh is located in the north-west part of India about 250 km north-west of Delhi. Eighty-three patients of Takayasu arteritis were registered with us during the period

from 1972 to 1990. The majority of the patients came from the neighboring states of Punjab (30), Haryana (11), Chandigarh itself (9), Himachal Pradesh (9), and Uttar Pradesh (6). The rest came from other states some of which were distant. As is shown in Table 1, the majority of the patients were between 20–30 years. There were 51 females with a male to female ratio of 1:1.6. All the patients had undergone a detailed clinical evaluation. The clinical history was recorded with special emphasis on the mode of onset, duration and severity of symptoms, hypertension if present and associated disorders like tuberculosis, gout, diabetes mellitus, hyperlipoproteinemias, and autoimmune disorders. The family history of hypertension, similar disease or history suggestive of cardio-cerebro-vascular episodes were recorded. Detailed examinations were carried out with special emphasis on determining blood pressure in all the four limbs with appropriate sized cuffs, symmetry of arterial pulses, bruit over aorta and its main branches, cardiomegaly, signs of cardiac or renal failure, ocular fundii and any evidence of tuberculosis.

The investigations included complete hemogram, urinalysis, fasting and post prandial blood sugar, blood urea, serum-creatinine, cholesterol, VDRL and electrolytes. Immunological investigations including rheumatoid factor, antinuclear antibody, complement, blast transformation to various specific and nonspecific antigens and lymphocyte subsets were carried out in some of the patients [14] and is detailed elsewhere in this supplement. The Mantoux test was also done. Suitable material was examined to confirm tuberculosis whenever suspected. Rapid sequence intravenous urography (IVU) was done in 54 patients for initial screening for renovascular hypertension. Aortography was done in 72 which confirmed the diagnosis of Takayasu arteritis. The remaining 11 patients were in the age range of 17 to 41 years with typical clinical findings of abnormal pulses, bruit and hypertension strongly suggestive of Takayasu arteritis. Thus they were included on clinical criteria alone. Five patients had Takayasu arteritis confirmed histologically after surgery or at postmortem examination.

Table 1. Age and sex distribution of patients of Takayasu arteritis as seen in Chandigarh, India

Age group (years)	Males (*n*)	Females (*n*)	Total	
			n	%
0–10	1	2	3	3.6
10–20	6	14	20	24.0
21–30	14	22	36	43.3
31–40	8	8	16	19.2
41–50	1	5	6	7.2
51–60	2	0	2	2.4
Total	32	51	83	100.0

Male : female ratio 1 : 1.6
Age at diagnosis (range) 5–53 years (mean ± S.D. 26.9 ± 9.7)

Table 2. Physical signs in Takayasu arteritis in 83 patients seen at Chandigarh, India

Signs	Cases (*n*)	%
Anemia	29	35
Hypertension	67	81
Abdominal bruit	31	37
Extra-abdominal bruit	21	25
Valvular lesions (total)	8	10
Aortic regurgitation	3	4
Mitral regurgitation	3	4
Aortic stenosis	1	1
Mitral stenosis	1	1
Congestive cardiac failure	12	14
Hemiplegia	6	7
Paraparesis	1	1
Takayasu's retinopathy	5/22	22
Hypertensive retinopathy	55	67
Grade I	6	7
Grade II	35	43
Grade III	7	9
Grade IV	7	9

Results

Presenting symptoms and clinical evaluation

The commonest mode of presentation was hypertension ($n = 50$) or related symptoms of headache ($n = 40$) and dyspnea ($n = 24$), syncope/giddiness ($n = 20$), palpitation ($n = 16$), visual disturbances ($n = 11$), and nausea and vomiting ($n = 9$). Weight loss ($n = 7$), stroke ($n = 7$), and arthralgia ($n = 4$) were some of the other prominent symptoms in these patients. Two patients who had hemoptysis were confirmed to have pulmonary artery involvement in Takayasu arteritis. An attempt was made to identify the time of onset of Takayasu arteritis as determined either by the development of specific symptoms like fever, arthralgia, limb claudication, visual disturbances, syncope, stroke, angina, hemoptysis or heart failure or the clinical findings of hypertension, asymmetry of pulses, aortic incompetence, aneurysm, or cardiac failure. It is important to emphasize here that the exact onset of Takayasu arteritis as described for the prepulseless phase was very difficult to define in the majority of our patients who commonly presented at the pulseless stage and had very little evidence of active inflammation at presentation. The details of the physical signs in these patients are summarized in Table 2. It is noteworthy that the abnormality of arterial pulses and the bruit over abdominal (37%) or extra-abdominal great vessels (25%) were the most helpful clinical clues to suspect Takayasu arteritis. Neck and upper limb pulses (carotid 16%, subclavian 36%, brachial 38%, and radial 46%) were absent or diminished in many of the patients. In addition the abnormality of the lower limb pulses were also noticeable as these were absent or diminished (femoral 20%, popliteal 21%, posterior tibial and dorsalis pedis 20% each) in quite a few.

General investigation

Anemia was present in 60 patients (mild 46 and moderate 14). Erythrocyte sedimentation rate (done

Table 3. Vascular involvement in Takayasu arteritis on angiography[a] in 72 patients seen at Chandigarh, India

	(*n*)	%
Ascending aorta	8	11
Arch of aorta	14	19
Descending thoracic aorta	12	17
Abdominal aorta	57	79
Subclavian artery (R:L)	14:40	19:56
Carotid artery (R:L)	5:12	7:17
Celiac artery	2	3
Superior mesenteric artery	9	13
Renal artery (R:L)	42:44	58:61
Inferior mesenteric artery	7	10
Iliac artery (R:L)	10:8	14:11
Pulmonary artery[b]	4	45

[a] Aortic arch not studied in 6
[b] Pulmonary angiography done in 9
R, Right; *L*, left

in 69) was elevated between 21–40 and over 40 mm in the 1st h in 19 and 27 patients, respectively. Twelve patients were azotemic with raised serum creatinine above 2.0 mg/dl in 11 of these. The Mantoux test was positive in 20 of 44 patients in whom it was done. Left ventricular hypertrophy as determined by the voltage criterion and the ST-T segment changes on ECG was present in 52/83 (63%) patients. Cardiomegaly, defined as cardiothoracic ratio of 50% or more, was present in 29 cases (35%) Intravenous urography was suggestive of renovascular hypertension in 45 of 54 (83%) patients studied.

Angiographic studies

Vascular involvement on angiography

A total of 72 patients underwent flush aortography through the femoral route. Aortic arch could not be studied in 6 patients. Nine patients, in addition, had pulmonary angiography done. The frequency of involvement of various vessels is summarized in Table 3. The angiographic patterns revealed a wide variety of lesions. Narrowing or stenosis of major arteries was the commonest finding seen in 66 patients (92%) and was associated with post stenotic dilatation in 16 (22%). Irregularity of the vessel wall, total vascular occlusion and dilatation without proximal stenosis were seen in 50 (69%), 26 (36%) and 18 (25%) patients. Calcification of wall of aorta was seen in 3 (4%) being marked in 1 and the aneurysms were seen in 5 (7%) of the patients.

Anatomic types

Four types of patterns of Takayasu arteritis were recognised according to the distribution of the vascular lesions. Type I (n = 8, 10%) involved the aortic arch and its branches alone, type II (n = 25, 30%) involved the descending thoracic and abdominal aorta, and type III (n = 46, 55%) had the combined features of Type I and II. Any of these groups along with the involvement of the pulmonary artery was classified as type IV (n = 4, 5%) (Figs. 1–4). As pulmonary angiography was performed only in 9 patients in our series, it is quite possible that the number of patients with pulmonary artery involvement is underestimated. Six patients had angina pectoris and documented coronary artery involvement in 2 patients.

Complication of Takayasu arteritis

The four major complications of Takayasu arteritis, i.e., hypertension, (n = 67/83, 81%) retinopathy (5/22, 22%), aneurysm formation (5/72, 7%) and aortic regurgitation (3/83, 5%), were graded according to the criterion used by Ishikawa [2]. Nine patients (11%) had none of these complications (stage I) and 19 patients (23%) had only one of these and that too in milder form (stage IIa). In 50 patients (60%), although having only one of these complications, it was rather severe (stage IIb). Five patients (6%) were in very advanced stages of the disease (stage III) with more than one complication established.

Treatment

Antihypertensive-drug therapy was the mainstay of treatment in the majority of our patients (67, 81%). Some required treatment for associated congestive cardiac failure, anaemia and renal failure. Antitubercular treatment was given to 6 patients (7%) for associated tuberculosis. Glucocorticosteroids (GCS) were used only in five patients. As it was difficult to ascertain the inflammatory/active stage of Takayasu arteritis in our patients, GCS were not used very often in view of inherent side effects. Surgery done in 10 patients included nephrectomy (3), autotransplantation of kidney (3) and revascularisation surgery (4). Percutaneous transluminal angioplasty of renal artery was done in 2 patients with success.

Long term follow-up

Development of complications (n = 10) in 49 Takayasu arteritis patients who were available for follow-up was studied. Renal failure developed in six (13%) and congestive heart failure in four (9%). Neurological deficits developed in two patients, and aortic regurgitation and gross visual impairment in one each. Some of the patients had more than one complication. Eleven patients died during follow-up. The common modes of death were heart failure (n = 4), renal failure (n = 2), and cerebral hemorrhage (n = 1). The cause of death was probably acute mycoardial infarction in one and was not certain in the remaining 3 patients. The period between the diagnosis of Takayasu arteritis and death

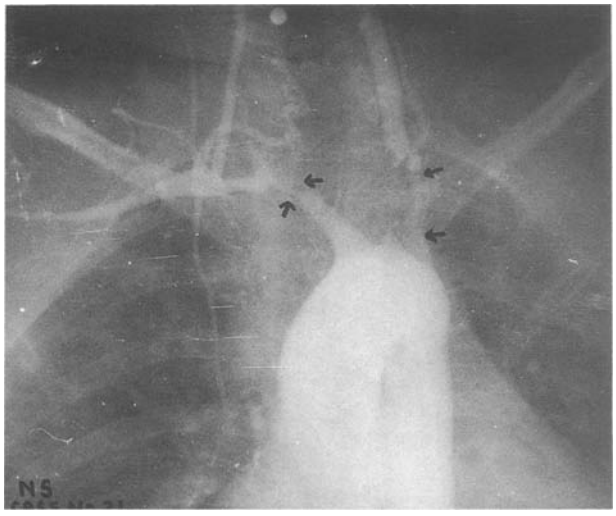

Fig. 1. Occlusion of the left subclavian artery and the right common carotid artery, irregularity and narrowing of left common carotid artery and right sub-clavian artery (*arrows*) (Type I)

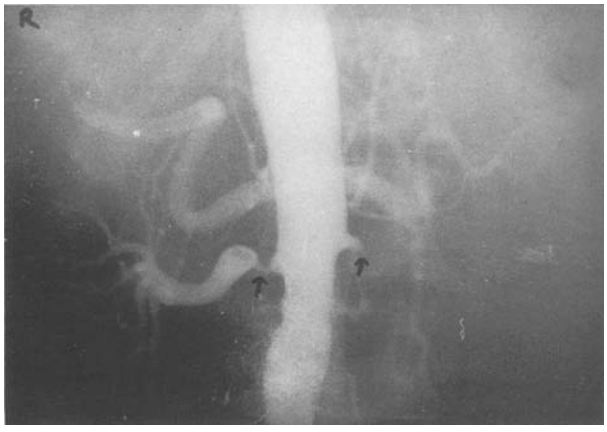

Fig. 2. Right renal artery stenosis with post-stenosis dilatation, and complete occlusion of the left renal artery (*arrows*) with irregularity and narrowing of infrarenal part of the aorta (Type II)

ranged from 4 to 69 months (mean 39 months). It is important to appreciate that six patients of even stage IIb and III disease (as above) survived for 4–5 years, which was attributed to effective antihypertensive drug therapy.

Discussion

The clinical profile of Takayasu arteritis as seen in the North west region of India is presented in this study but is fairly representive of this disease in India. The disease is known to occur in a wide spread area over the globe being more common in Japan, India, South East Asia and Mexico [1–15]. The disease has been reported from Western [1], Eastern [9, 11, 13], Northern [7, 8, 10, 14, 21] as well as Southern [12] India. The majority of our patients came from the northwestern states of India with some coming from other parts. The

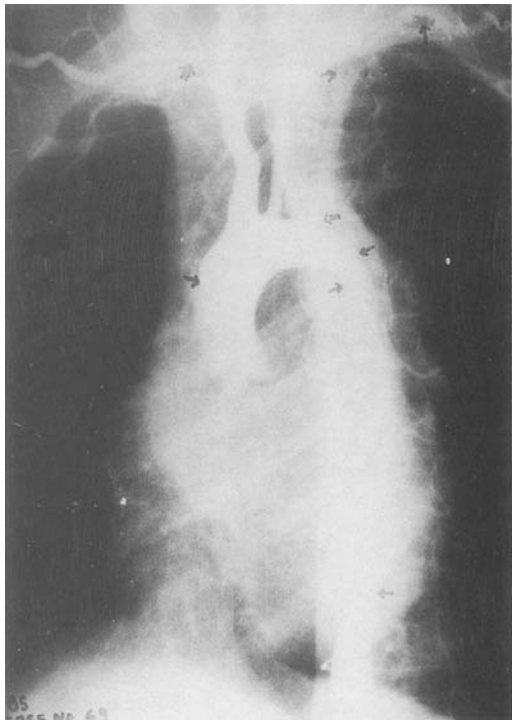

Fig. 3. Stenosis and irregularity of the right and left subclavian arteries (*double-lined arrows*), irregularity and narrowing of the ascending aorta, arch of aorta and descending thoracic aorta (Type III)

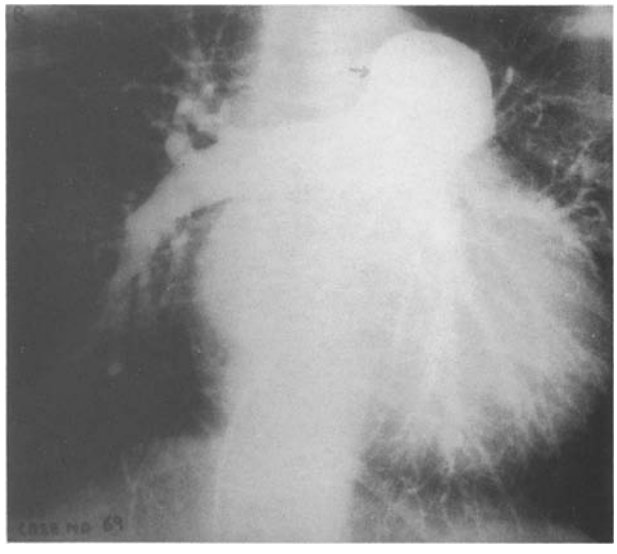

Fig. 4. Marked dilatation of main pulmonary artery (*arrows*). In this case the arch of aorta, abdominal aorta bilateral subclavian and bilateral renal arteries were also involved (Type IV)

selective regional distribution of Takayasu arteritis over the globe brings in the genetic theory of its pathogenesis which was gained much recognition recently. We however did not find any family having more than one member affected by Takayasu arteritis as has been reported by Numano et al. [16, 17].

The average age of the patients at presentation in this study was 26.9 years and in the majority of patients ranged from 10 to 30 years. Similar findings have been reported by other Indian workers [7, 8, 12] as well as workers from Japan [2] and other countries [4, 6, 15, 18]. In this study, we did not observe such a marked female preponderance as described from Japan [2], USA [15], and Singapore [6]. Sen et al. from Bombay [1] and Chhetri et al. from eastern India [19] described a female: male ratio of 3:1, as is also noticed by Piyachon from Thailand [5]. The reasons for such a difference in sex distribution in various studies are not clear.

Contrary to the observations in reports both from Mexico [15] and Japan [20] that Takayasu arteritis is commonly characterized by the onset of constitutional symptoms like fever, anorexia, night sweats, weight loss, arthralgias, arthritis, only 16% patients in this study had constitutional symptoms. Other reports from India have also not observed systemic symptoms of activity as common phenomenon in Takayasu arteritis even in early stages [7, 10, 12]. It is possible that these are related to the host differences as supported by the different HLA associations of the disease [16].

The important clinical manifestations of Takayasu arteritis are related to either obstructive aortoarteritis or to systemic hypertension. Systemic hypertension was present at the time of initial evaluation in 81% of our patients. While similar observations have been reported by other workers from India [7, 8, 12], USA [15], Thailand [5], and Singapore [6], Ishikawa from Japan [2], and De-yu et al. from China [4] reported much lower occurrences of hypertension in Takayasu arteritis. Hypertension in Takayasu arteritis is multifactorial and commonly results from stenosis of renal arteries. The other mechanism postulated include the marked narrowing of aorta, abnormal function of aortic and carotid sinus baroreceptors and reduced elasticity of the aortic and arterial walls. In the present study, eight patients with hypertension did not reveal any renal artery stenosis. Five of these had marked narrowing and two had diffuse irregularity of aorta. In one patient, the mechanism of hypertension was not clear. In 38% patients, blood pressure in one upper limb was not recordable or was much lower than the pressure in the contralateral upper or the lower limbs. Absent or weak pulses in one or more limbs or the neck provided a strong clinical clue to this disease as was seen in 73% patients in this study and has also been reported by Malhotra et al. (40%) [7], Sharma et al. (52%) [8], Lupi-Herrera et al. (96%) [15], and Hall et al. (50%) [18]. Such abnormality of pulses result from the thickening of the intima, fibrosis and scarring of media and occasionally due to superimposed thrombosis.

Vascular bruits indicating the partial obstruction or stenosis of the vessel underneath were audible over the neck and abdomen in about one third of the patients. Thus inspite of bruit being a very important clinical indicator, its absence does not exclude the diagnosis. Similar observations have been documented both in children [10] and adults [7] from India, but Teoh et al. [6], Lupi-Herrera et al. [15], and Hall et al. [18] reported a much higher (86–95%) occurrence of vascular bruit in their patients.

Congestive cairdac failure (CCF) was a prominent presenting feature in 12 (14%) patients of this study and was related to development of hypertension and possibly myocardial disease as was also described by Talwar et al. [21]. This form of presentation is much more common in children suffering from Takayasu arteritis. The mean age of those presenting with congestive heart failure was 34.3 ± 10.5 which was much older than that reported by Lupi-Herrera et al. [15] and Shrivastava et al. [10]. Many of these patients had associated left ventricular hypertrophy on electrocardiographic examination. These findings support the fact that hypertension was mainly responsible for development of CCF in the majority of our patients. Aortic regurgitation was present in three patients, and mitral regurgitation was present in another three. The frequency of valvular lesions associated in Takayasu arteritis reveals great variation even within India, whereas Subramaniyan et al. [12] reported aortic regurgitation in 24% of their patients Das et al. [13] reported in only 11%. De Yu et al. [4] also reported the presence of aortic regurgitation in 12.9% of their patients. Thus our experience is more like that of Lupi Herrerra et al. (7%) [15], Kar et al. [11] (8.5%), Teoh et al. [6] (8.3%) and Hall et al. [18] (9.3%). However, Subramaniyan et al. found a very high incidence of aortic regurgitation in their patients [12]. Two of the five patients who had angina were documented to have coronary artery involvement on aortography or autopsy. The one diagnosed on autopsy also showed inflammation of endocardium, myocardium and pericardium with granuloma formation as has been described by Talwar et al. in their endomyocardial biopsy studies [21].

The neurological manifestations in our patients were similar to what has been described in the literature from India and Japan and resulted from involvement of the carotid or vertebral arteries or as a consequence of hypertension. Takayasu's retinopathy is uncommon with us, compared to the Japanese literature and is possibly because of the lesser frequency of involvement of the aortic arch in our patients. It was seen in

only 5 of the 22 patients who had undergone detailed opthalmic hemodynamic studies and had fluorescein angiography. All these patients had carotid artery stenosis or occlusion which resulted in this form of ischemic retinopathy. Similar to that described by Kar et al. [11], Maity et al. [9] and Lupi-Herrera et al. [15] hypertensive retinopathy was common in our patients too because of the development of long-standing and often severe hypertension. In this regard it is worth mentioning that renal artery involvement was a common finding in our patients explaining the higher incidence of hypertension. Gradually, 10% of patients with severe hypetension and renal artery disease (unilateral/bilateral) went on to develope renal insufficiency. We found intravenous urography (IVU) to be of great help as a screening procedure in predicting correctly the existence of ischemia of the kidney in over 80% of our patients who had undergone IVU. Similar findings have been reported from other parts of our country as well [7, 10].

Aortography confirmed the diagnosis of Takayasu arteritis and delineated the exact nature and exent of the vascular involvement. The Majority of our patients (55%) had diffuse involvement as has also been described from other parts of our country [12] and Mexico [15]. This is a significant difference compared to patients in Japan where much greater involvement of aortic arch and its vessels has been documented [2]. We in India see frequent involvement of the renal arteries in contrast to the Japanese studies which show left subclavian as the most common site of involvement [2, 7, 12]. Pulmonary artery involvement was also much less frequent in this study and other Indian studies as compared to the studies by Ishikawa et al. [2], Lupi Hererra et al. [22], and Kozuka et al. [23]. Routine pulmonary angiography, however, was not performed in the majority of the cases.

Elevated erythrocyte sedimentation (ESR) rate was seen in over two-thirds of our patients even at pulseless stages of disease. The significance of this finding is not quite clear as many of these patients with elevated ESR continue to show no other evidence of active inflammatory disease. For the purpose of clinical staging and outcome we classified our patients as proposed by Ishikawa [2] and found that the distribution of patients in various categories was actually similar to what he described, stage IIb being the commonest stage at presentation.

All our hypertensive patients received antihypertensive drugs. Most of the time the response to the drugs was good and blood pressure was well-controlled in the majority of the patients, a response also observed by others. As against the reports by Lupi-Herrera et al. [15] the outcome of surgery in carefully selected patients was quite rewarding in our hands. We tried to select our patients at a stage when there was little evidence of active inflammatory disease and the disease was more or less "burnt out". Hall et al. [18] and Shalhamer et al. [24] from the USA and Kar et al. [11] from India also reported similar experiences with surgery in Takayasu arteritis.

Takayasu arteritis is associated with increased premature deaths and several major nonfatal events on follow-up. All the deaths in this series occurred within the first 6 years after the diagnosis was established. Cardiac failure was the single most common mode of death. The mode of death as well as the nonfatal events, the most common being renal failure, were directly related to the anatomic type and severity of the disease and were to a large extent predictable at initial evaluation itself. Although prognosis in a given individual was difficult, it appeared that the severe form of Takayasu arteritis (states IIb and III) clearly carried a worse prognosis. Hypertension was probably an important determinant of the increased risk of morbidity and mortality. Overall, the disease appears to be slowly progressive and fortunately may remain static for long periods in some patients whose control of hypertension and other complications has been well managed.

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