

Clinical Manifestations of Takayasu Arteritis in India and Japan— New Classification of Angiographic Findings

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ABSTRACT

In this retrospective review 102 Indian and 80 Japanese patients with Takayasu arteritis were compared in regard to their clinical manifestations and angiographic findings. Regardless of nationality, most patients were initially affected in their teens or twenties. Japanese patients were female in a larger ratio compared with the ratio in India. Clinically, the two groups exhibited several different features. More Japanese patients were found to be pulseless ($P < 0.01$) whereas many Indian patients were hypertensive ($P < 0.01$). Inflammatory conditions in Japanese patients were more severe ($P < 0.01$) and tended to be more prolonged than those in the Indians. More Japanese patients suffered from aortic regurgitation ($P < 0.01$), but Indians suffered from hypertension ($P < 0.01$). Angiographic findings revealed that the aortic arch and its branches were mainly involved in Japanese patients (type I, IIa) whereas the abdominal aorta and its branches were mainly involved in Indian patients (type IV). However, the diffusely involved type (type V) was the one most commonly found in both countries. From the analyses of vascular lesions in both Indian and Japanese patients, 510 and 396, respectively, different progressions of vasculitis are speculated. In Japanese patients, vasculitis generally occurs in the ascending aorta, the aortic arch, and/or its branches and extends into the thoracic and abdominal aorta, subsequently forming various complicated lesions with prolonged inflammatory activity. On the other hand, in Indian patients, vasculitis generally occurs in the abdominal aorta involving renal arteries, subsequently extending into the thoracic aorta within one or two decades, simple vascular lesions being formed. Data analysis suggests that this morbid condition progresses differently in India and Japan, in spite of some common etiologic factor(s).

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Introduction

Takayasu arteritis (TA) is a chronic arteritis that mainly affects the aorta and its major branches including coronary and pulmonary arteries.¹⁻⁷ This inflammatory condition causes narrowing, stenosis, occlusion, dilatation, or aneurysm of the involved arteries.⁸ Therefore, clinical manifestations vary greatly depending on the affected arteries,^{1-4,9,10} making early diagnosis difficult. In Japanese cases, the involvement of the aortic arch and its branches is common,^{4,11} resulting in pulselessness of the upper extremities, and so "pulseless disease"¹² is another common name for this morbid condition. Furthermore, the dilatation of the ascending aorta causes annulo-aortic dilatation and aortic regurgitation,¹³⁻¹⁷ whereas the involvement of abdominal and thoracic aorta and/or renal arteries causes typical aortic coarctation and/or renal hypertension.

Although more than eighty years have passed since the first report of this morbid condition as characteristic of unusual retinal changes by Takayasu in 1908,¹⁸ the etiology of this morbid condition is still unknown. Many epidemiologic studies have revealed that TA is mostly observed in Asian and South American countries.¹⁹ Since the first conference of the Japan-Korea Cooperative Survey on TA (May 1989), which was supported by a grant from the Japanese Ministry of Education, the comparative study of the disease has continued among several Asian countries, Yajima et al¹¹ reported, for the first time, comparative studies on TA among Japanese, Korean, and Indian patients based up to 1992 and revealed several different characteristic clinical features. Afterward, we studied more profiles of Indian cases, which more clearly revealed differences between Indian and Japanese patients. In this analysis, we report the differences in the clinical manifestations and angiographic findings between Indian and Japanese TA patients.

Materials and Methods

This retrospective study included 102 Indian and 80 Japanese patients with TA in each country, according to a mutually established protocol. The Indian cases were reviewed at Nehru Hospital, which is attached to the Postgraduate Institute of Medical Education and Research, Chandigarh; Japanese cases were reviewed at Tokyo Medical and Dental University Hospital, Tokyo.

In all cases, the following comparisons were made between Indian and Japanese patients: (1) sex and age of onset, (2) follow-up period, (3) clinical manifestations, and (4) angiographic findings.

Initial clinical signs and symptoms, laboratory findings, electrocardiographic findings, main complications, and causes of death were compared between Indian and Japanese patients.

We have classified the involved area of TA according to Nasu's classification⁸ in Japanese patients. However, the international conferences of comparative studies on TA among Asian and South American countries in 1993 and 1994, supported by a grant from the Japanese Ministry of Education, Science, Sports and Culture, have revealed that the involvement of the thoracic and/or abdominal arteries is more common in Asia and South America than in Japan and that this involvement and its clinical manifestations and progression of the disease require awareness. From this background, in 1994, we devised a new classification of TA as shown in Figure 1. Type I primarily involves the branches from the aortic arch. Type IIa involves the ascending aorta, aortic arch, and its branches. Type IIb involves the ascending aorta, aortic arch and its branches, and thoracic descending aorta. Type III involves the thoracic descending aorta, abdominal aorta, and/or renal arteries. Type IV affects only the abdominal aorta and/or renal arteries. And type V combines the features of both type IIb and IV. Furthermore, the involvement of the coronary or pulmonary artery should be designated as C (+) or P (+).

In this study, angiography (including digital subtraction angiography) was performed in the 102 Indian and 80 Japanese patients and the findings were classified according to the new classification.

The results of patients' ages, follow-up periods, and laboratory findings were expressed as mean value \pm standard deviation, and statistical analyses were made by nonpaired t-test (using Student's or Welch's method) or Fisher's exact probability test. A P value <0.05 was considered significant.

Results

Sex and Age

Diagnoses were established or reaffirmed at the institutions mentioned above. It is interesting that

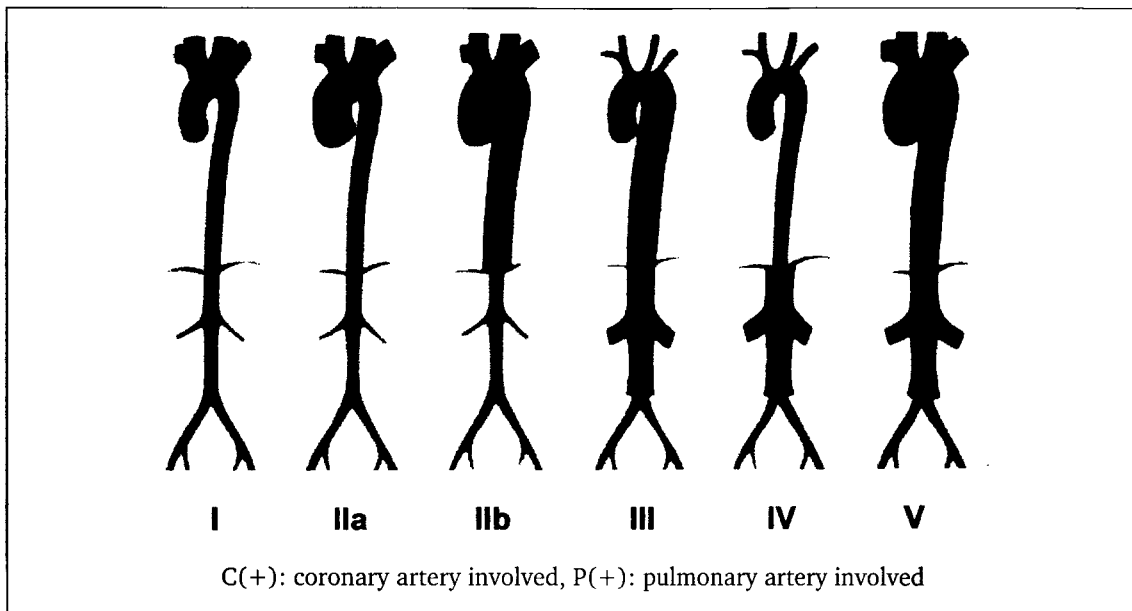


Figure 1. New Classification of Takayasu arteritis on Takayasu Conference in 1994

only 4% of the Japanese patients were male; the sex ratio was 1:26 (Table I). In contrast, more than one third of the Indian patients were male, the ratio being 1:1.7. This difference of sexual distribution ($P < 0.01$) is epidemiologically quite unique. It is equally interesting that the mean age of the Indian patients is about one decade younger than that of the Japanese patients ($P < 0.01$).

Follow-up Period

We estimated the onset age as the time when typical signs and symptoms appeared or seemed to have appeared for the first time. Age at diagnosis or confirmation represents the age when each patient first consulted us. In Japanese patients, mean onset age was less than thirty years old, and they were diagnosed within a decade after the

Table I
Age and Sex of Patients

	Japan		India		P Value
	n (%)	Age	n (%)	Age	
Male	3 (4)	44.0 ± 13.0 (29–52)	38 (37)	30.9 ± 10.7 (14–60)	NS
Female	77 (96)	37.2 ± 14.4 (12–71)	64 (63)	26.6 ± 9.3 (14–50)	$P < 0.01$
Total	80	37.1 ± 14.3 (12–71)	102	28.2 ± 10.0 (14–60)	$P < 0.01$

Table II
Follow-up Period

	Japan	India	P Value
Age at onset	28.2 ± 12.6		
Age at diagnosis	37.1 ± 14.3	28.2 ± 10.0	P < 0.01
Duration	24.3 ± 11.5		
Follow-up period	15.5 ± 6.6	2.2 ± 2.3	P < 0.01

first appearance of clinical signs (Table II). Japanese patients were followed-up for fifteen years or more. In Indian patients, age at diagnosis or confirmation was one decade younger than that of Japanese patients. However, the mean follow-up period was only two years.

Initial Clinical Signs or Symptoms

Among the clinical signs and symptoms exhibited, some patients suffered from two or more symptoms. Table III shows the initial clinical signs or symptoms. Among clinical symptoms, dizziness and vertigo were more frequently observed in Japanese patients ($P < 0.05$), while headache was a common symptom in Indian patients ($P < 0.01$). In clinical signs, pulselessness or laterality of radial pulsation was a frequent finding in Japan ($P < 0.01$); in contrast, hypertension was the single most dominant sign in Indian patients ($P < 0.01$).

Laboratory Findings

Erythrocyte sedimentation rate (ESR) and serum total protein concentration and serum albumin concentration were elevated in Japanese patients compared with those in Indian patients ($P < 0.01$) (Table IV). However, hemoglobin concentration did not differ.

Electrocardiographic Findings

Left ventricular hypertrophy was a main finding in each country but was significantly more frequent in Indian patients ($P < 0.05$) (Table V). One third of the patients were within normal limits.

Angiographic Classification

Table VI and Figure 2 show the comparison of angiographic findings revealing some significant differences between Japanese and Indian patients. Although more than half of the patients, both Indian and Japanese, were the combined type (type V) note that types I and IIa were dominant in Japanese patients ($P < 0.01$), while to the contrary, type IV was dominant in Indians ($P < 0.01$). Of special note is that cases of type III were recognized in Indian patients but not among the Japanese.

Anatomic Distribution of Lesions

The anatomic distribution of vascular lesions presented in Table VII shows 448 in Indian patients and 340 in Japanese. The involvement of the ascending aorta, thoracic descending aorta, brachiocephalic artery, vertebral artery, and common carotid artery was observed more frequently in the Japanese than in the Indian patients ($P < 0.01$, $P < 0.05$, $P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively). Subclavian arteries were the frequent sites of vascular lesions in both countries. Abdominal vascular lesions, especially renal arteries, were more frequently observed in the Indian patients than in the Japanese ($P < 0.05$, $P < 0.01$, respectively).

Characteristics of Vascular Lesions

Narrowing (stenosis $< 25\%$) lesions were more frequently observed in Indian patients as compared with the Japanese ($P < 0.01$) (Table VIII). In contrast, stenotic lesions and the subsequent

Table III
Initial Clinical Signs and Symptoms

	Japan	India	P Value
Pulselessness	32	1	P<0.01
Dizziness/vertigo	14	9	P<0.05
Hypertension	10	50	P<0.01
Vascular pain	10	10	NS
Fatigue/weakness	8	9	NS
Syncope	4	13	NS
Fever	6	2	NS
Headache	3	32	P<0.01
Visual disturbance	2	5	NS
Claudication	0	5	NS
Hemiplegia	1	4	NS
Raynaud phenomenon	0	5	NS
Others	20	8	
Total	110	153	

Others: including paresthesia, shoulder stiffness, vascular bruit, elevated erythrocyte sedimentation rate, aortic elongation in chest radiograph, etc.

Table IV
Laboratory Findings

	Japan (n)	India (n)	P Value
ESR (mm/hr)	52.1 ±42.5 (66)	33.3 ±21.7 (98)	P<0.01
Total Protein (g/dL)	7.4 ±0.9 (62)	6.6 ±0.9 (80)	P<0.01
Albumin (g/dL)	4.0 ±0.5 (61)	3.6 ±0.6 (82)	P<0.01
Hemoglobin (g/dL)	12.1 ±1.7 (67)	11.9 ±1.9 (100)	NS

Table V
Electrocardiographic Findings

	Japan (n=64)	India (n=102)	P Value
Left ventricular hypertrophy	29	63	P<0.05
Left axis deviation	2	0	NS
Left atrial enlargement	2	1	NS
Subendocardial ischemia	3	7	NS
Old myocardial infarction	2	0	NS
Arrhythmia (including heart block)	4	1	NS
Right ventricular hypertrophy	1	0	NS
Right atrial enlargement	0	1	NS
Within normal limits	31	31	NS
Total	74	104	

Table VI
Comparison of Angiographic Findings
(Takayasu Conference in 1994)

	Japan	India	P Value
I	19 (24%)	7 (6.9%)	P<0.01
IIa	8 (10%)	1 (1.0%)	P<0.01
IIb	10 (13%)	6 (5.9%)	NS
III	0 (0%)	3 (2.9%)	NS
IV	1 (1.3%)	29 (28%)	P<0.01
V	42 (52%)	56 (55%)	NS
Total	80	102	

Table VII
Anatomical Distribution of Vascular Lesions

	Japan	India	P Value
Ascending aorta	34	9	P<0.01
Aortic arch	14	19	NS
Descending thoracic aorta	36	29	P<0.05
Brachiocephalic artery	22	15	P<0.05
Vertebral artery (right/left)	26 (16/10)	10 (3/7)	P<0.01
Subclavian artery (right/left)	67 (25/42)	86 (26/60)	NS
Common carotid artery (right/left)	68 (29/39)	30 (11/19)	P<0.01
Abdominal aorta	38	75	P<0.05
Renal artery (right/left)	27 (13/14)	122 (59/63)	P<0.01
Celiac artery	1	7	NS
Superior mesenteric artery	5	15	NS
Inferior mesenteric artery	2	3	NS
Iliac artery (right/left)	0	28 (16/12)	P<0.01
Total	340	448	

development of lesions, such as occlusion and dilatation, were more frequently observed in Japanese patients (P<0.01, P<0.01, P<0.01, respectively).

Main Complications

In each TA patient, several complications appeared (Table IX, Fig. 3). Hypertension was the most common complication in both countries. However, a higher frequency was observed in the Indian patients (P<0.01). It is noteworthy that aortic regurgitation was a frequent complication in Japanese patients (P<0.01).

Causes of Death

Six Japanese and 10 Indian patients died from congestive heart failure, sudden cardiac death, chronic renal failure, cerebrovascular disease, or unknown causes (Table X). There were no remarkable differences or tendencies among them.

Discussion

In 1908, Takayasu M. reported the first case of TA as an interesting case exhibiting a peculiar retinal

fundus.¹⁸ Later it was confirmed that this characteristic fundus resulted from ischemic changes in retinal vasculature. Shimizu and Sano described this morbid condition precisely and named it as "pulseless disease" in 1951.¹² It was revealed that the main clinical manifestations of TA were stenosis and/or obstruction of the aortic arch and its main branches to the upper extremities and cervical lesions. In fact, the chief complaints of TA patients in Japan at their first visit were vertigo, dizziness, visual disturbance, and/or pulselessness. Angiographic analyses revealed a high percentage of involvement of the ascending aorta, aortic arch, and its branches.^{2,4}

Since 1991, we have started comparative studies of TA among Asian countries to search for the etiology of this morbid condition.²⁰ The genetic factor is one of the main targets of this study because TA is characterized by genetic differences among populations. For example, our human lymphocyte antigen (HLA) studies confirmed the higher frequency of the haplotype HLA24-B52-DR2 in TA than in healthy normal controls.²¹⁻²⁵ Now more data have been collected further indicating the genetic factor(s) as one of the causative factors of this disease.

Table VIII
Characteristics of Vascular Lesions

	Japan	India	P Value
Narrowing	90 (23%)	287 (56%)	P<0.01
Stenotic	139 (35%)	84 (16%)	P<0.01
Occlusive	88 (22%)	67 (13%)	P<0.01
Dilatational	69 (17%)	59 (12%)	P<0.01
Aneurysm	10 (2.5%)	13 (2.5%)	NS
Total	396	510	

Table IX
Main Complications

	Japan	India	P Value
Hypertension	44/75 (59%)	90/101 (89%)	P<0.01
Cerebrovascular disease	3/53 (5.6%)	11/96 (11%)	NS
Retinopathy	15/100 (30%)	74/102 (73%)	P<0.01
Aortic regurgitation	35/66 (53%)	7/94 (7.5%)	P<0.01
Congestive heart failure	6/60 (10%)	13/100 (13%)	NS

Table X
Causes of Death in the Study

	Japan	India
Congestive heart failure	1	2
Sudden cardiac death	3	2
Chronic renal failure	0	1
Cerebrovascular disease	1	0
Unknown	1	5
Total	6 (7.5%)	10 (9.8%)

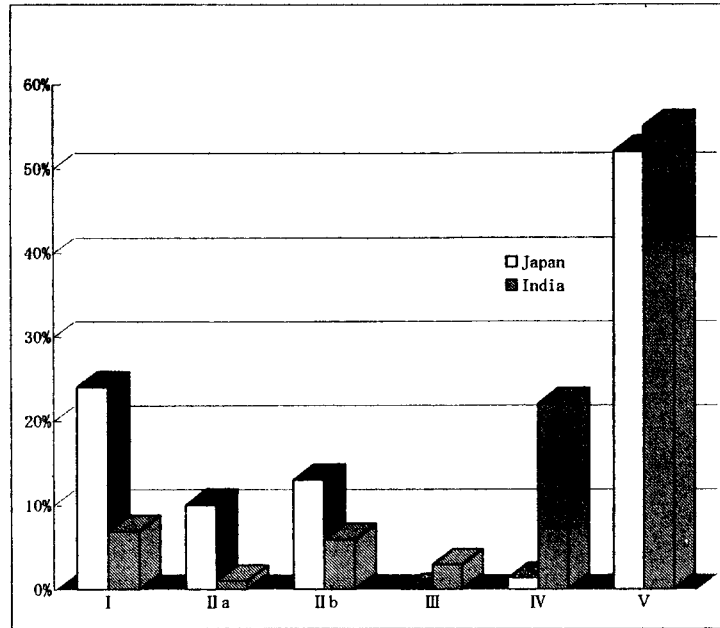


Figure 2. Comparison of angiographic findings.

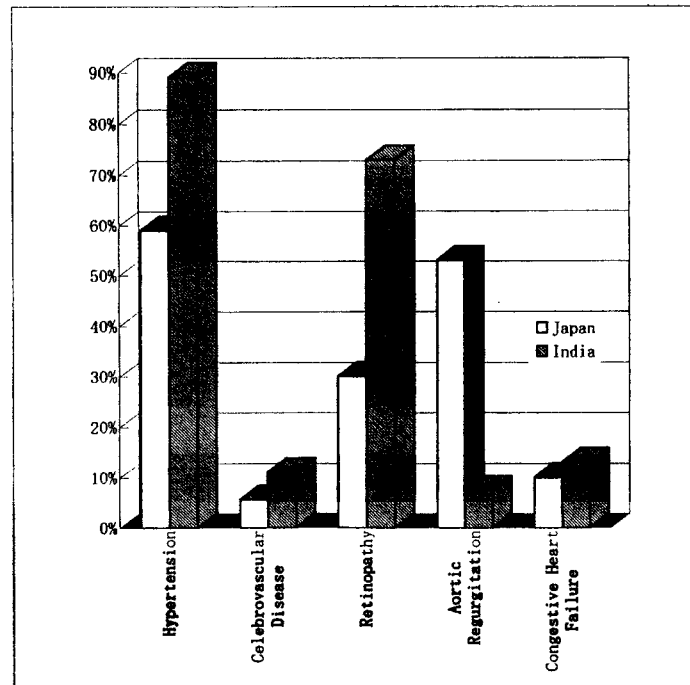


Figure 3. Main complications.

At the same time, from these analyses, we have been surprised to learn of the many different characteristic clinical manifestations of this morbid condition among Asian populations.^{11,26-30} For instance, 89% of the patients are female in Japan.^{31,32} However, we learned that this sex ratio diminishes in the Asian countries west of Japan.^{27,28,30} Note, therefore, that in the present study, 96% of the patients were female, while 37% of the Indian patients were male with a mean age about one decade younger.

As to the clinical manifestations, while dizziness, vertigo, and pulselessness were common in the Japanese, headache and hypertension were common in the Indians. The former reflects the higher frequency of involvement of the aortic arch and its branches in Japanese patients, while in the latter, hypertension likely caused the headaches. According to the laboratory findings in both countries, ESR, serum total protein concentration, and serum albumin concentration were elevated in Japanese patients. These findings show that inflammatory activity and the subsequent increase in production of protein were higher in the Japanese. Electrocardiographic findings showed that left ventricular hypertrophy was more frequent in Indian patients, owing probably to the higher frequency of hypertension.

These different manifestations suggest the different involvement of vascular sites. In fact, angiographic analyses confirmed that the involvement of the ascending aorta, the aortic arch, and the brachiocephalic, vertebral, and common carotid arteries was mainly observed in Japanese patients. On the other hand, the involvement of the abdominal aorta and renal arteries was mainly observed in Indian patients, although the combined type was common in both Japanese and Indian patients. These results agree with the higher frequency of aortic regurgitation, pulselessness, dizziness, and vertigo in Japanese patients and the hypertension, retinopathy, and headache in Indian patients. From this background, we decided to use the new classification of angiographic analyses instead of Nasu's because type III in the new classification involves both the thoracic and abdominal aorta, recognizing an increased spread of the vessels affected. This type was not defined in Nasu's classification. In fact, in the present study we did not find this type in the Japanese patients, though we did find a few cases in the Indian patients (2.9%).

We noted that narrowing lesions were frequently observed in Indian patients. On the other

hand, stenotic lesions and the subsequent development of occlusion and dilatation were frequently observed in Japanese patients. These findings indicate that the morphology and spread of vascular lesions vary according to the inflammatory activity in Japanese patients.

Hypertension was the most common complication in both countries but to a greater extent in India. Hypertension in the Indian patients may have been mainly of renal vascular origin. On the other hand, aortic regurgitation due to the dilated aortic root is known to be a frequent and serious complication of TA that sometimes causes fatal congestive heart failure.^{4,11,13-17,33} Note that aortic regurgitation is not common in Indian patients.

Conclusion

In Japanese patients, TA may occur primarily in thoracic aorta and/or its branches and extend into the abdominal aorta. Afterward, various complicated lesions of vasculitis may form with prolonged inflammatory activities. On the other hand, in Indian patients, this morbid condition may occur primarily in the abdominal aorta, including involvement of renal arteries, and extend into the thoracic aorta within one or two decades, where, consequently, simple vascular lesions may form. At present, we do not know why these differences occur and we are studying this puzzle in relation to the genetic factor(s). We are now collecting data from Asian and South American countries under the new classification, which will be reported in the near future.

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