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Patterns of Symptoms and Prognosis in Occlusive Thromboaortopathy (Takayasu's Disease)

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Ninety-five Japanese patients with Takayasu's disease were classified according to four patterns of severity of symptoms in the period from the onset of symptoms to diagnosis. Included were pattern A in 34 patients with a plateau course after the insidious onset of symptoms, pattern B in 18 patients with a decrescendo course after the sudden onset of severe symptoms, pattern C in 5 patients who had no severe symptoms during the years between the early and late periods of severe symptoms and pattern D in 38 patients with a crescendo course after the onset of symptoms and the following period of years of no severe symptoms. Fifteen patients died during the prospective follow-up period of 8.6 ± 6 years (mean ± SD) after admission, but 12 had had patterns C and D and the remaining 3 had had patterns A and B. The cardinal signs and symptoms are given in detail, particularly those at the onset. These data should aid in early diagnosis and prediction of the prognosis in Takayasu's disease.

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Signs and symptoms in patients with Takayasu's disease (occlusive thromboaortopathy), a disease of worldwide distribution (1,2) and geographic variations in its clinical aspects (3–6), vary considerably with regard to severity, duration and quality; hence, the physician sees no definite pattern. The modes of presentation, in particular that of the onset, are so various that early diagnosis in the prepulseless phase is often not feasible (7,8). In addition, most patients have an asymptomatic or mildly symptomatic stage of variable duration in the clinical course (9–11). Thus, the diagnosis of Takayasu's disease is often delayed until the advanced stage when severe cardiovascular complications attributable to the disease may develop and the prognosis is often poor (11,12). This disease essentially is a chronic inflammatory arteriopathy of unknown origin, and the site of occurrence is the aorta or its main branches, or both (13). Association with pulmonary artery involvement occurs in about half of these patients (10,11).

The classification of patterns of symptoms according to the course of their severity in the period from onset to diagnosis was prepared after an analysis of the histories obtained in 95 patients with Takayasu's disease. The relation of these patterns to other clinical features, with special reference to prognosis, is discussed. The cardinal signs and symptoms of the disease, particularly as related to an early diagnosis, are given attention.

Methods

Patient selection. During the 27.8 year period from May 1957 to March 1985, there were 104 Japanese patients with Takayasu's disease who were admitted to the Third Department of Internal Medicine, Kyoto University, where the diagnosis of the disease was established or reaffirmed. In 95 of the 104 patients, supravalvular and abdominal aortography or autopsy, or both, were performed. The present report concerns these 95 patients, including 86 women and 9 men. The average age (± SD) at the time of first admission was 32.5 ± 11.0 years (range 16 to 64). All patients had narrowing or occlusion in some region of the aorta or its main branches, or both.

Among the three anatomic types, defined with regard to location of the arterial lesions (9), there were 30 doses of the aortic arch type, 2 of the descending aorta type and 63 of the extensive type, that is, a combination of the first two types. An erythrocyte sedimentation rate (Westergren) of 20 mm in 1 hour or greater, that is, the active stage of the disease (14), was evident in 60 patients (63%). Of the 95 patients, the pulmonary circulation was studied in 91, using pulmonary arteriography, cardiac catheterization and perfusion lung scanning in 76, and using perfusuion lung scan-

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ning alone in 15. Of the 91 patients, 52 (57%) had involvement of the pulmonary artery and 24 of these 52 had one or more lobar arterial occlusions or their equivalent.

Follow-up. Each patient was prospectively followed up for observation periods ranging from 2 months to 27.8 years from May 1957 through March 1985, the average (± SD) being 8.6 ± 6.0 years. Of the 95 patients, 70 were examined by me at least every 6 weeks after the first admission. Of the remaining 25 patients, 21 were followed up in this manner for the first 5 years; after that time, 14 were examined at least once a year and 7 were mainly followed up by a referring physician. The final four patients were followed up only by a referring physician after a few years of outpatient care by me. Information on the condition of these 11 patients was obtained once a year in letters sent by the referring physicians or the patients, or both, or by telephone.

History taking. In all but three patients, history taking during admission was carefully done by me and was usually repeated two or more times in each patient.

Criteria for severity of symptoms. The severity of subjective symptoms was estimated according to restrictions on physical activity and was scored as follows: 0 = no restriction of ordinary physical activity; 4 = moderate restriction of ordinary physical activity (patients can do desk work but can barely perform manual labor or suffer from considerable inconvenience); 8 = marked restriction of ordinary physical activity because of severe symptoms (patients can barely perform desk work or suffer from considerable inconvenience; 12 = bed rest. The severity of symptoms between adjacent grades was further scored. For example, slight restriction of ordinary physical activity was scored as 2. The grading was determined at the time of history taking in each patient. These criteria have remained unchanged since 1967 (Fig. 1).

Classification of patterns of severity of symptoms. The 95 patients were retrospectively classified into four groups according to the patterns of severity of symptoms recorded in the histories from the onset of symptoms of Takayasu's disease to the first diagnosis of the disease. *Pattern A* included 34 patients (36%) with a plateau course after the insidious onset. *Pattern B* included 18 patients (19%) with a decrescendo course after the sudden or fairly sudden onset of severe symptoms. *Pattern C* included five patients (5%) with a decrescendo-plateau-crescendo course in which there were no severe symptoms in the years between the early and late periods of severe symptoms. *Pattern D* included 38 patients (40%) with a plateau-crescendo course in which symptoms rapidly became severe after the onset and a period of years with no severe symptoms (Fig. 1).

Classification of severity of complications. According to the evidence and severity of four complications attributable to the disease at the time when the diagnosis was established or reaffirmed, patients were classified into four groups (Groups I, IIa, IIb and III) during the admission

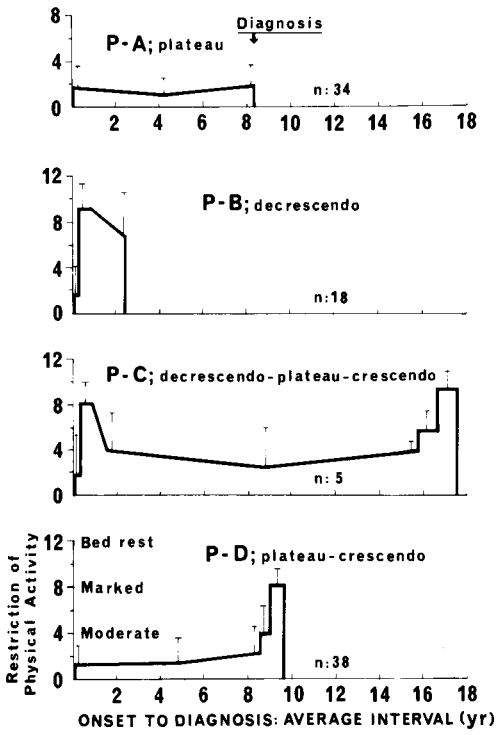


Figure 1. The four patterns (P) of severity of subjective symptoms in the period from the onset of symptoms to first diagnosis in 95 patients with Takayasu's disease. The scale on the **ordinate** indicates score of severity of symptoms. The **vertical bars** indicate the standard deviation of the mean. The average interval (± SD) from the onset of symptoms to first diagnosis was 8.4 ± 8.7, 2.5 ± 4.4, 17.6 ± 13.1 and 9.7 ± 6.9 years in patterns A, B, C and D, respectively.

except for the first 14 patients classified after discharge as follows:

Group I—uncomplicated Takayasu's disease, with or without involvement of the pulmonary artery.

Group II, single complication—presence of one of the following complications together with uncomplicated Takayasu's disease: 1) Takayasu's retinopathy; 2) secondary hypertension; 3) aortic regurgitation; or 4) aortic or arterial aneurysm. This group was further classified according to the severity of these complications into *Group IIa* (mild or moderate complication) and *Group IIb* (severe complication).

Group III, multiple complications—two or more complications together with uncomplicated Takayasu's disease.

More detailed criteria for this classification were as reported (11,12) and these have been unchanged since 1967, except for a slight modification concerning the severity of Takayasu's retinopathy in 1981 (12).

Statistical analysis. Statistical comparisons were made using the one-way analysis of variance (15) (Table 1), the

Table 1. Patterns of Symptoms, Clinical Course, Number of Patients With Early Diagnosis and Death

Classification of Patterns of Symptoms	No. of Patients	Average Age (±SD) (yr)			Length of Follow-up After Admission (yr)	No. of Patients (%)		
						Onset to First Diagnosis		
		At Onset	At First Diagnosis	At First Admission		Within 12 Months	Asymptomatic Period of More than 1 Year	Death During Follow-up
Pattern A (plateau pattern)	34	21.8 ±8.2	30.2 ±11.7	31.8 ±10.6	8.1 ±5.1	3 (9)	15 (44)	2* (6)
Pattern B (decrescendo pattern)	18	21.6 ±6.5	24.1 ±8.8	27.1 ±8.1	8.5 ±5.0	13 (72)	2 (11)	1 (6)
Pattern C (decrescendo-plateau-crescendo pattern)	5	20.2 ±7.8	37.8 ±16.1	42.0 ±15.4	2.4 ±3.0	0	3 (60)	2 (40)
Pattern D (plateau-crescendo pattern)	38	23.9 ±8.6	33.6 ±10.5	34.6 ±10.9	9.9 ±6.9	0	11 (29)	10 (26)
Total	95	22.5 ±8.0	30.8 ±11.5	32.5 ±11.0	8.6 ±6.0	16 (17)	31 (33)	15 (16)

*Of the two, one died with uterine cervix carcinoma.

Student's *t* test and the chi-square method with the Yates' correction for continuity. The cumulative survival rate was estimated using the life table method (16). All values are reported as mean ± standard deviation except where specified.

Results

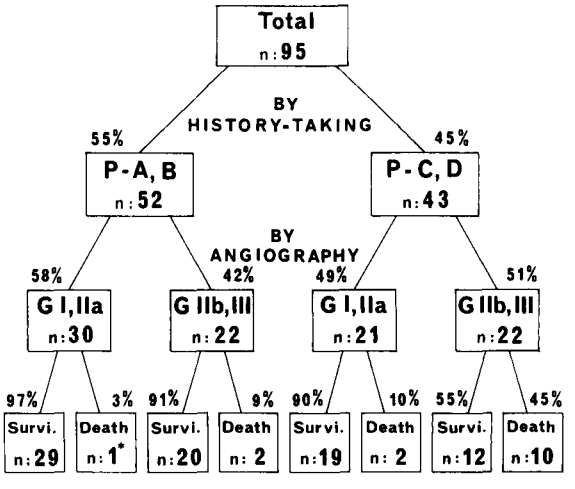
Clinical classification. Figure 1 shows the classification of four patterns in the course of severity of symptoms in the period from the onset of symptoms to the first diagnosis of Takayasu's disease. The average interval from the onset to first diagnosis was 8.3 ± 8.2 years in the 95 patients. In the early phase, the average duration of severe symptoms in patients with patterns B and C was 0.5 year (range 0.1 to 2.8) and 0.6 year (range 0.2 to 1.0), respectively. In the late phase, the average duration of severe symptoms in patients with patterns C and D was 1.0 year (range 0.2 to 3.3) and 0.7 year (range 0.1 to 3.0), respectively.

Clinical course. The average age at the time of the onset of signs or symptoms, or both, of Takayasu's disease in the 95 patients with patterns A, B, C and D was 22.5 ± 8.0 years (range 8 to 40). One-way analysis of variance showed no significant difference in mean values of age at that time among the four patterns. Of the 95 patients, 16 were diagnosed within 12 months from the onset of symptoms. These 16 patients included 13 (72%) of the 18 with pattern B and 3 (9%) of the 34 with pattern A. On the other hand, 12 of the 15 who died during the follow-up period had patterns C and D. The average age at the time of death in these 15 patients was 44.0 years (range 21 to 70). The average duration of the asymptomatic period in the 31 patients was 8.6 ± 6.4 years (Table 1).

Relation of patterns of symptoms and complications to prognosis. For further analysis of the prognosis, patients with pattern A or B and those with pattern C or D were, respectively, classified into combined Groups I (no complications) and IIa (mild or moderate complication) and combined Groups IIb (severe single complication) and III (multiple complications). Of the 15 who died during the follow-up period, 10 had pattern C or D and were in Group IIb or III. The total number of patients with this combination was 22. In contrast, among the 22 patients who had pattern A or B and were in group IIb or III, only 2 died (Fig. 2).

The 43 patients with pattern C or D had a significantly

Figure 2. Relation of patterns (P) of symptoms and complications to the prognosis in 95 patients with Takayasu's disease. G = groups; Survi. = survival; * = died with uterine cervix carcinoma at age of 70 years.



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poorer survival rate after the first admission than did the 52 patients with pattern A or B (12 year survival rate (mean ± SEM) 70.4 ± 4.1% versus 91.1 ± 6.8%; $p < 0.01$). The 6 year survival rate of the 22 patients in Group IIb or III with pattern C or D was significantly lower than that of the other 73 patients (54.9 ± 7.1% versus 97.0 ± 1.5%; $p < 0.001$) (Fig. 3). There was no significant difference between the average age at the time of onset for the 22 patients (pattern C or D and Group IIb or III) (25.0 ± 8.9 years) and that for the other 73 patients (21.8 ± 7.6 years). However, there was a significant difference between the average age (at the time of first diagnosis and of first admission for the 22 patients (respectively, 37.9 ± 12.4 years and 39.6 ± 12.6 years) and those for the 73 patients (respectively, 28.6 ± 10.3 years and 30.5 ± 9.7 years) (both $p < 0.001$).

During the follow-up period, corticosteriod therapy was usually prescribed in the active stage of the disease, and oral anticoagulant agents were often given. For symptomatic therapy, digitalis, antihypertensive agents and antibiotic drugs were frequently used. Of the nine patients who underwent surgical repair of the aorta or its main branches, three died within 4 weeks (after application of a patch graft to the abdominal aorta in one, aneurysmectomy of the ascending aorta in one and apicoaortic bypass in one). Unilateral nephrectomy without vascular reconstructive surgery was done in two patients.

Among the 95 patients, 21 (62%) of the 34 patients with pattern A, 15 (83%) of the 18 patients with pattern B, 3 (60%) of the 5 patients with pattern C and 24 (63%) of the 38 patients with pattern D had alleviation of subjective symptoms during the follow-up period. Symptoms in the remaining 13 (unchanged in 10, aggravated in 3) 3, 2 and 14 (unchanged in 2, aggravated in 12) patients with these respective patterns either were unchanged or worsened. The severity of subjective symptoms in 10 patients with pattern B, 1 patient with pattern C and 15 patients with pattern D was decreased from a score of 8 or more to 4 or less during the follow-up period. In eight patients in Group I the disease was in the inactive stage and no therapeutic intervention was considered necessary; seven of these had pattern A and one had pattern B.

Comparison of early and late symptoms. Table 2 shows the signs and subjective symptoms during the first 12 months compared with those during the last 12 months in the period from the onset of symptoms to first diagnosis of the disease. The major sign was pulselessness or pulsus differens in the upper limbs or an unobtainable blood pressure or significant blood pressure difference in the brachial arteries. This major sign had been detected incidentally, regardless of the diagnosis of the disease, by physicians or nurses or patients themselves in most of the listed patients. Severe symptoms with or without signs during the first 12 months occurred in 23 patients (patterns B and C), and during the last 12 months in 43 patients (patterns C and D). Of the former 23, eight (35%) had unexplained high fever (38°C or higher) of 3 weeks or longer duration, but this did occur in not the latter 43 patients ($p < 0.005$). In contrast, only 2 (9%) of the 23 patients (patterns B and C) had severe disability due to dyspnea and palpitation, but 18 (42%) of the 43 patients (patterns C and D) had severe disability ($p < 0.025$). Fatigability of the limbs was usually mild, and was severe in ony three patients.

Misdiagnoses. In 34 (36%) of the 95 patients, their condition had been incorrectly diagnosed at other institutions in the period from onset to the first diagnosis of Takayasu's disease, including 19 instances of misdiagnosis during the first 12 months from the onset of symptoms. The misdiagnoses included hypotension in 12 patients, rheumatic fever in 6, rheumatoid arthritis in 5, valvular disease in 3, sepsis in 2 and other diseases in 6. The misdiagnoses of rheumatic fever, valvular disease and sepsis were made during the first 12 months. In contrast, misdiagnosis of hypotension in 8 of the 12 patients was made after the first 12 months. Rare but specious tentative misdiagnoses were dilated cardiomyopathy in one patient and hypertrophic cardiomyopathy in another. These two patients had "normal" or low blood pressure of the limbs caused by significant narrowing or occlusion of the aorta and its main branches

Figure 3. Comparison of survival rates after the first admission in patients with patterns A and B (**open circles**) and patterns C and D (**closed circles**) and 6 year survival rate for patients with a combination of pattern C or D and Group IIb (severe single complication) or III (multiple complications) (**closed triangles**). The number of patients alive at the beginning of each follow-up interval is indicated in parentheses. The **vertical bars** indicate the standard error. p = probability; pts = patients.

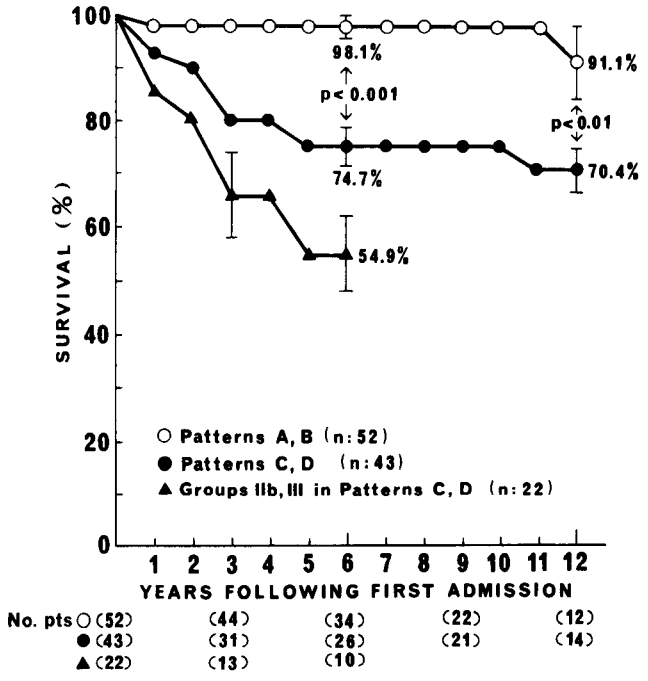

Table 2. Comparison of Signs and Symptoms During the First and Last 12 Months From Onset of Symptoms to First Diagnosis

Signs and Symptoms	First 12 months (n=95) No.	%	Last 12 Months (n=79)* No.	%	p Values†
Major sign‡	15	15.8	50	63.3	<0.005
Minor signs					
High blood pressure	7	7.4	18	22.8	<0.01
Unexplained high ESR or fever (low or high grade)	21	22.1	10	12.7	NS
Major local symptoms					
Easy fatigability or pain in the limbs	36	37.9	42	53.2	NS
Upper limbs	26		35		
Lower limbs	8		6		
Upper and lower	2		1		
Neck pain	12	12.6	7	8.9	NS
Transient amaurosis or blurred vision	15	15.8	21	26.6	NS
Syncopal attacks or TIAs	10	10.5	10	12.7	NS
Dyspnea and/or palpitation	17	17.9	36	45.6	<0.005
Other					
General fatigue	30	31.6	36	45.6	NS
Headache	30	31.6	26	32.9	NS
Dizziness or vertigo	14	14.7	24	30.4	<0.025
Shoulder stiffness	10	10.5	9	11.4	NS
Arthralgia	10	10.5	3	3.8	NS
Back pain	7	7.4	7	8.9	NS
Nausea and/or vomiting	6	6.3	3	3.8	NS
Anorexia	5	5.3	7	8.9	NS
Cough	5	5.3	4	5.1	NS
Hemoptysis	4	4.2	2	2.5	NS
Tinnitus	4	4.2	8	10.1	NS
Chest pain	3	3.2	8	10.1	NS
Abdominal pain	3	3.2	2	2.5	NS
Weight loss	3	3.2	2	2.5	NS
Aphthous stomatitis	3	3.2	2	2.5	NS
Lumbago	2	2.1	2	2.5	NS
Claudication of jaw	2	2.1	0	0	NS
Myalgia	1	1.1	0	0	NS
Asymptomatic signs	7	7.4	4	5.1	NS
Bed rest or severe disability	23	24.2	43	54.4	<0.005

*Sixteen patients diagnosed within 12 months from the onset are not included; †chi-square method. ‡Pulselessness, pulsus differens in upper limbs, unobtainable blood pressure or significant blood pressure difference in brachial arteries. ESR = erythrocyte sedimentation rate; NS = not significant; TIAs = transient ischemic attacks.

despite proximal hypertension attributable to Takayasu's disease.

Discussion

Patterns of symptoms. The signs and symptoms of Takayasu's disease have been protean and variable, particular in quality (7,8). However, the symptoms could be classified into the four patterns when assessed according to the clinical disability and course, regardless of the type of symptom. The patterns of symptoms, as well as the early prepulseless and late pulseless phases (7) and complications attributed to the disease (11), are all aspects of the natural history of Takayasu's disease. At the time of first admission, more than half the patients with patterns A (plateau course after insidious onset) and B (decrescendo course after sudden onset of severe symptoms) were in the active stage of disease and more than one-third had a severe single complication or multiple complications. Therefore, some patients with pattern A or pattern B may progress to pattern D (plateau-crescendo course) and pattern C (decrescendo-plateau-crescendo course), respectively, if diagnosis and treatment are further delayed.

Onset. Patients with Takayasu's disease can have both insidious and sudden onset of signs or symptoms, or both. It has been reported (10) that the duration of initial acute

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symptoms is about 3 months, and that some patients at this stage already have an advanced clinical state. In the present series of 95 patients, 72 (76%) (patterns A and D) had an insidious onset and 23 (24%) (patterns B and C) had a sudden or considerably sudden onset of severe symptoms, with the average duration being 0.5 year. During the first 12 months from the onset of symptoms, the major sign was detected independently of the diagnosis in 15 (16%) of the 95 patients. Of the 16 whose disease was diagnosed within 12 months of onset, 8 (50%) had a severe single complication or multiple complications, and 5 of these 8 had no pulselessness at the time of the first diagnosis of the disease or at the first admission. This evidence suggests that patients with Takayasu's disease often have an early but pulseless phase and an "early prepulseless" but advanced phase of the disease.

Factors related to the delay in diagnosis. A delay in the diagnosis of Takayasu's disease may be related to: 1) misdiagnosis, 2) masked Takayasu's disease as a result of corticosteroid therapy to misdiagnosed diseases or concomitant complications, 3) nondetection of mild easy fatigability in the limbs, and 4) presence of an asymptomatic state (9–11) and changing pattern of symptoms (11). An early diagnosis was not made in most patients with pattern A or D who had cardinal signs or symptoms (major sign, minor signs or major local symptoms in Table 2) during the first 12 months from the onset of symptoms. The possibility of Takayasu's disease was apparently not considered because severe subjective symptoms were absent and pertinent studies of the onset of this disease have rarely been documented.

Patterns of symptoms and complications. In a previous report on prognosis (12), it was shown that the 10 year survival rate for patients in Groups IIb (severe single complication) and III (multiple complications) was significantly lower than that for patients in Groups I (no complications) and IIa (mild or moderate complication). In the present series, among 18 patients with pattern B, 9 belonged to Group IIb or III and had had severe subjective symptoms at the time of first diagnosis, but only 1 of these 9 had died during the follow-up period. This favorable result may be due to the fact that in all but one of these nine patients the diagnosis had been made and treatment begun within 1 year from the onset of symptoms. The most morbid combination of clinical features in Takayasu's disease was pattern C or D and Group IIb or III (Fig. 3).

Implications. In patients with Takayasu's disease, there are four patterns of severity of subjective symptoms seen from the time of onset to diagnosis. The signs and symptoms in the early phase of the disease after its onset are not always vague. Not only the major sign, but also a combination of the minor signs or major local symptoms (Table 2), may be a key reminder of Takayasu's disease when physicians are taking a detailed history or are repeating history taking after the physical examination. If these signs or symptoms occur in women and begin at a young age, the likelihood of an early tentative diagnosis of the disease increases, although these are not in themselves diagnostic criteria. Recognition of both the dynamic patterns of symptoms and groups for severity of complications that influence the prognosis should lead to an early diagnosis of Takayasu's disease.

References

1. Ask-Upmark E. On the "pulseless disease" outside of Japan. Acta Med Scand 1954;149:161–78.
2. Lande A, Bard R, Rossi P, Passariello R, Castrucci A. Takayasu's arteritis: a worldwide entity. NY State J Med 1976;76:1477–82.
3. Joffe N. Aortitis of obscure origin in the African. Clin Radiol 1965;16:130–40.
4. Deutsch V, Wexler L, Deutsch H. Takayasu's arteritis: an angiographic study with remarks on ethnic distribution in Israel. Am J Roentgenol 1974;122:13–28.
5. Lande A, Rossi P. The value of total aortography in the diagnosis of Takayasu's arteritis. Radiology 1975;114:287–97.
6. Ishikawa K. Takayasu's disease. In: Robicsek F, ed. Extracranial Cerebrovascular Disease: Diagnosis and Management. New York: Macmillan, 1986:387–94.
7. Strachan RW. The natural history of Takayasu's arteriopathy. Quart J Med 1964;33:57–69.
8. Bonventre MV. Takayasu's disease, revisited. NY State J Med 1974;74:1960–7.
9. Nakao K, Ikeda M, Kimata S, et al. Takayasu's arteritis: clinical report of eighty-four cases and immunological studies of seven cases. Circulation 1967;35:1141–55.
10. Lupi-Herrera E, Sánchez-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE. Takayasu's arteritis: clinical study of 107 cases. Am Heart J 1977;93:94–103.
11. Ishikawa K. Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). Circulation 1978;57:27–35.
12. Ishikawa K. Survival and morbidity after diagnosis of occlusive thromboaortopathy (Takayasu's disease). Am J Cardiol 1981;47:1026–32.
13. Nasu T. Takayasu's truncoarteritis: pulseless disease or aortitis syndrome. Acta Pathol Jpn 1982;32(suppl 1):117–31.
14. Ishikawa K. Matsuura S. Occlusive thromboaortopathy (Takayasu's disease) and pregnancy: clinical course and management of 33 pregnancies and deliveries. Am J Cardiol 1982;50:1293–300.
15. Snedecor GW, Cochran WG. One-way classifications, analysis of variance, samples of unequal sizes. In: Statistical Methods. Ames, IA: Iowa State University Press, 1976:277–9.
16. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chronic Dis 1958;8:699–712.