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Takayasu arteritis in Korean children: Clinical report of seventy cases

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Summary. Seventy cases of Takayasu arteritis in Korean children are reported. There were 57 females and 13 males (male-to-female ratio; 1:4.4). The youngest patient was a 3-year-old female. Family history was positive in one patient. The most common chief complaints on admission were dyspnea, headache, palpitation, and edema which were due to hypertension and congestive heart failure. Hypertension was seen in 65 out of 70 patients (92.8%). The abdominal aorta, thoracic aorta, and renal arteries were the most commonly involved sites in these children. Two patients had nephrotic syndrome. The frequency of positive tuberculin reaction was much higher in children with Takayasu arteritis compared with the general population, and the intensity of the reaction was also stronger. The majority of the patients required immediate medical treatment to control congestive heart failure due to hypertension at initial presentation. When ESR was elevated, corticosteroid was administered. Surgical treatment showed good results in six out of ten cases. Percutaneous intraluminal angioplasty was effective for lowering the blood pressure in six out of nine cases. In three cases, restenosis occurred and angioplasty was repeated in two cases.

Key words: Takayasu arteritis – Aortitis syndrome – Renovascular hypertension – Percutaneous transluminal angioplasty

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Introduction

Since Takayasu described a case of a pulseless disease with retinal changes in 1908 [1], many similar cases have been reported in the literature. The disease occurs at any age but rarely in childhood. The cause is still unknown.

Patients and methods

During the past 26 years, from 1962 to 1988, 70 cases of Takayasu arteritis have been encountered in children at Seoul National University Hospital and six other hospitals in the Seoul area.

The diagnosis was based on the clinical and aortographic findings.

Results

Age and sex

The age and sex distribution are shown in Table 1.

Clinical manifestations

The chief complaints are summarized in Table 2.

The most common chief complaints on admission were dyspnea, headache, edema, and palpitation. All of these symptoms were due to hypertension. Hypertension was seen in 65 out of 70 patients (92.8%). Most of them had congestive heart failure.

Thirteen cases showed fainting spells or seizures because of the narrowing of the carotid artery. The duration of the symptoms prior to admission varied from several weeks to several years.

Laboratory findings

The laboratory findings are summarized in Table 3.

Table 1. Age and sex distribution

Age	Male	Female	Total
0–4		6	6
5–9	6	25	31
10–15	7	26	33
Total	13	57	70

M:F = 1:4.4

The youngest patient was a 3-year-old female. Of the 70 patients 57 (81.4%) were female, and the male-to-female-ratio was 1:4.4. Females were more prevalent in all age groups. There is one patient whose aunt also had Takayasu's arteritis.

Table 2. Chief complaints (n = 70)

Chief complaints	n
Dyspnea	37
Headache	29
Palpitation	22
Edema or puffy face	22
General weakness	16
Vomiting	13
Fainting spells or seizure	13
Cough	11
Anorexia	11
Chest discomfort	5
Intermittent claudication	5
Abdominal pain	4
Blindness or visual disturbance	3
Weight loss	2
Epistaxis	2
Irritability	1
Lower extremity pain	1
Paralysis of lower extremities	1
Joint pain	1
Hemiplegia	1

Table 3. Laboratory findings

Hb < 11.0	20/69	29.0%
WBC ≥ 10,000	27/69	39.1%
ESR ≥ 20	37/66	56.0%
Urine: albumin (+)	17/67	25.3%
RBC (+)	4/65	6.2%
LE Cell	0/26	0%
ASO ≥ 250 U	10/45	22.2%
VDRL (+)	1/33	3.0%
TB Skin test (+)	56/62	90.3%

Anemia and leukocytosis were present in a mild degree in one-third of the cases. Fifty-six percent of the cases showed a slight-to-moderate increase in the erythrocyte sedimentation rate, with a gradual decrease revealed by a follow-up check. The total serum protein slightly decreased in 7 of the 33 cases studied. An electrophoretic pattern showed a decrease in albumin and an increase in gammaglobulin. Proteinuria was present in one-fourth of the cases.

Table 4. Tuberculin-positive rate in the general population, children with other diseases and with Takayasu arteritis

Age (years)	General population		Children with other diseases	Children with Takayasu arteritis
	1970	1980	(1983–85)	(1962–88)
0–4	9%	5%	8%	100%
5–9	26%	13%	13%	87%
10–14	54%	32%	20%	90%
Total (No. tested)	29% (4657)	12% (2573)	13% (727)	90% (62)

The intensity of the reaction was stronger in children with Takayasu arteritis than in other children (Table 5).

Table 5. Intensity of the positive reaction

	Positive reactors (n)	Mean diameter (mm)	
Children with other diseases	66	15 × 15	
Children with Takayasu arteritis	41	31	23 × 21
		7	Strong positive
		3	Positive

Table 6. HLA Antigens in patients with Takayasu arteritis

Case no.	HLA Antigens							
	A		B		C		DR	
1	24,	31	13,	w52				
2	24,	w33	7,	44			1,	w6
3	2,	24	w54,	w57	w1,	w3	4,	w6
4	3,	24	35,	51	w4		2,	w9
5	1,	w33	37,	44	w4		4,	w9
6	11,	24	7,	13	w3		1	
7	2,	30	w22,	w61			w6	
8	2		39,	w61	w3			
9	11,	30	13,	w62	w3			
10	30,	w33	14,	44				
11	2,	11	51,	60	1		2,	4
12	30		44		w7		w13	7

Two cases had nephrotic syndrome with Takayasu arteritis. One case showed focal and segmental glomerulosclerosis by renal biopsy. No LE cell was demonstrated in any of the 26 patients studied. An anti-streptolysin 0 titer of more than 250 Todd units was found in 10 out of the 45 patients studied. VDRL was reactive only in 1 out of the 33 cases tested. Antinuclear antibody was positive only in 1 out of 11 cases. The Mantoux test was positive in 90% of the cases, and most of them showed a strong reaction. This positive rate is significantly higher compared with the same age population in Korea (Table 4).

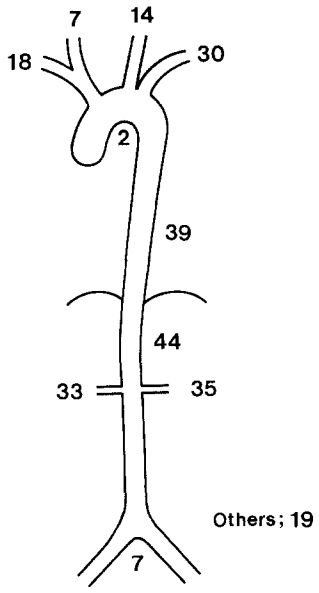

Fig. 1. Sites of lesions in the aorta in 70 cases

Among the 70 patients, 9 (12.9%) had tuberculosis and 3 others had a family history of tuberculosis among their parents or siblings.

HLA antigens were examined in 12 cases (Table 6). No statistically significant difference in the frequency of antigens could be demonstrated compared with the normal control because of the small sample size.

Aortographic findings

Aortography was performed in all of the 70 cases. The sites of involvement are shown in Fig. 1. The abdominal and thoracic aorta were most commonly involved, followed by the renal artery and subclavian artery. In one case there was a double renal artery, one part of which was stenosed. The left subclavian arteries were more frequently involved than the right (R:L = 18:30). We found one case in which the right coronary artery was involved. The aortic arch was relatively less involved in children compared to adults.

Treatment

In the majority of cases, the first required treatment was to control the congestive heart failure due to hypertension. For this purpose various antihypertensive drugs were used.

When ESR increased and C-reactive protein was reactive, corticosteroid was administered. When the TB skin test was strongly positive, INH was given with corticosteroid.

In ten cases, surgical treatment was done. One patient expired 30 h after the surgery, and one case showed remarkable improvement after surgery but expired 1 year after the operation. One case had renal failure. Six cases (60%) showed improvement by relieving the hypertension. In two cases nephrectomy was done.

Recently balloon angioplasty has been applied for nine of our patients, dilating 14 sites of narrowed lesions. All of them had severe hypertension and congestive heart failure and were in an inactive stage. Percutaneous intraluminal angioplasty was very effective for lowering the blood pressure in six out of nine cases. The effect was more prominent in short segmental lesions than in diffuse ones. In three cases, restenosis appeared, 4 months, 7 months, 3 years, respectively, after the angioplasty. Angioplasty was repeated in two cases and a by-pass graft was performed in one case.

Discussion

Although Takayasu arteritis occurs from early childhood, it is rare in children and no large series of cases in children has appeared in the pediatric literature [2]. The first case of Takayasu arteritis in Korean children was reported in 1963 [3]. Ten more pediatric cases were reported in 1967 [4].

According to the nationwide surveys in Japan, the peak age of Takayasu arteritis was between 20 and 30 years during the period of 1973–1975 but there has been a tendency for the peak age to shift upward with the peak age being between 30 and 40 years during the period of 1982–1984 [5]. The patients below 10 years of age occupied 1% (22/2, 148) of total patients in the former period but had decreased to 0.1% (3/2, 606) in the later period [5], and to 0.07% (3/3, 891) in 1988 (K. Koide, perso. communication, 1991). It appears that the incidence of Takayasu arteritis in children has been decreasing.

The preponderance of females in Takayasu arteritis was seen in all age groups in this series and the male-to-female ratio was 1:4.4. The sex incidence of Takayasu arteritis has geographic variations. The male-to-female-ratios reported in the literature were 1:8 in Japan [5], 1:2.8 in China [6], 1:3 in Thailand [7], and 1:1.4 in India [8].

Takayasu arteritis may involve any part of the aorta and its major branches. The abdominal aorta with or without renal artery involvement was the most commonly involved site in our patients, followed by the thoracic aorta. Because of these lesions, 65 out of 70 patients (92.8%) had hypertension. In many cases the acute general manifestations such as fever, malaise, or weakness were unrecognized and patients were brought to the hospital because of symptoms due to hypertension. It is possible that mild cases of

Takayasu arteritis had escaped clinical identification during childhood.

In reviewing the published cases of Takayasu arteritis in children, the abdominal aorta was the most frequently involved site [9, 10].

In Korea, Takayasu arteritis is the most common cause of renovascular hypertension in children. In a Korean study, 71% (15/21) of the renovascular hypertention was due to Takayasu arteritis [11]. Takayasu arteritis was also the leading cause of renovascular hypertension in South Africa [10] and in India [12].

We have experienced two cases of Takayasu arteritis associated with nephrotic syndrome. One case showed focal and segmental glomerulosclerosis by renal biopsy. There have been several reports on Takayasu arteritis associated with glomerulonephritis [13–18].

The Mantoux test was positive in 90% of our cases and the reaction was usually strong. This positive rate is significantly higher compared with the same age population in Korea.

Many previous authors have also reported the high positive rate of tuberculin reaction in patients with Takayasu arteritis [4, 10, 19–24]. In most of the reports, the patients were mostly adults, and it was considered that the positive rate was high because it was also high in the general population in those areas. But we can notice a significant difference in the positive rate of tuberculin reaction between the patients and general population, if we seperate the pediatric age group from adults.

In India, Kinare found associated active tuberculous inflammation in 12 out of 20 cases (60%) of Takayasu arteritis while it could be found only in about 10% of the general population [23]. In a Chinese series of 500 cases of Takayasu arteritis, a past history of tuberculosis was found in 29.8% and active lesions were found in 31.4% [6].

Some authors have noted high frequency of tuberculin-positive hypersensitivity in children with Takayasu arteritis. Wiggelinkhuizen and Cremin reported eight cases of Takayasu arteritis with renovascular hypertension in children, all of whom had strongly positive tuberculin reaction [10]. Milner et al. also reported six cases of Takayasu arteritis with severe hypertension in children, all of whom had strongly positive tuberculin reaction [25]. Rose and Sinclair-Smith reported sixteen autopsied cases of Takayasu arteritis. Tuberculosis was present in 6 out of 16 cases (37.5%), all of whom were 16 years of age or younger [24]. Morrison et al. demonstrated mycobacterial antigen using anti-BCG antibodies in diseased vessels of patients with Takayasu arteritis [26].

On the other hand, many authors have not noted any high frequency of positive tuberculin skin test in patients with Takayasu arteritis. In a North American series, only one of nine tested patients had a positive PPD skin test [27]. In Samantray's series in India, only 1 out of 45 cases showed a strongly positive Mantoux reaction [28].

It is possible that multiple genetic and environmental factors are involved in the pathogenesis of Takayasu arteritis. Many authors have suggested that Takayasu arteritis is an autoimmune disorder. Some reports described a circulating antibody directed against components of the human arterial wall [29] although other investigators fail to support these findings. Sagar et al. found higher lymphocyte blast transformation on exposure to purified human aortic extract in patients with Takayasu arteritis [30].

There is a possibility that various infections may play a role as initiating factors on the autoimmune mechanism. Tuberculous infection may play a role as one of the triggering factors in areas where tuberculosis is prevalent.

The possibility cannot be excluded of an underlying immune disorder favoring the development of both arteritis and tuberculosis or hypersensitivity to tuberculin.

The genetic factors in the pathogenesis of Takayasu arteritis have been studied by many investigators [31–33]. In our series one case had a family history of Takayasu arteritis, the patient's aunt having had the disease.

The haplotype *BW 52* has been associated with Takayasu arteritis in Japan [32, 33] and Korea [34].

We have examined HLA antigens in 12 cases and found only 1 with *BW 52*. Because of the small sample size, we could not find a significant difference compared to the general population. In an Indian series, the frequency of HLA B5 and HLA B21 was higher in patients with Takayasu arteritis [8].

We performed surgery in ten of our cases, all of whom had severe hypertension and were in an inactive phase. Six cases showed good results.

Pokrovsky and Tsyneshkin reported good results in 85.4% of cases 9 years after surgery for nonspecific aorta-arteritis [35]. Takagi et al. reported on long-term follow-up after surgical treatment for 30 cases. Twenty-three patients (77%) showed good results during the study period [36]. Ueno performed aortic or arterial reconstructive surgery in 77 cases, [37]. Early graft occlusion and late anastomotic failure occurred in approximately 50% in active cases while it occurred in 20% of inactive cases. The long-term prognosis, however, is guarded in severely hypertensive children even with surgical treatment because of the extensive vascular changes due to Takayasu arteritis [25]. Surgical treatment of Takayasu arteritis should be considered in selected cases after inflammatory aspects have been controlled.

Percutaneous transluminal angioplasty (PTA) has been applied for dilating stenotic lesion in Takayasu arteritis since 1980 [39–45]. We have performed PTA for 14 narrowed lesions in nine pediatric patients. PTA

was very effective in six of them. In three cases, restenosis occurred, 4 months, 7 months and 3 years, respectively, after the procedure. Longer periods of observation are needed to evaluate the long-term results of this procedure, but PTA offers an alternative to reconstructive vascular surgery to relieve the sereve hypertension and congestive heart failure in children with Takayasu arteritis. If restenosis occurs, PTA may be repeated or surgical treatment may be considered.

Conclusions

1. Takayasu arteritis was more prevalent in females than in males at all ages.
2. The abdominal aorta, the thoracic aorta, and renal arteries were the most commonly involved sites in these patients. Aortic arch involvement was less frequently seen in children. Hypertension was seen in 65 out of 70 patients (92.8%) and congestive heart failure due to hypertension was the most common presenting manifestation on admission.
3. Takayasu arteritis is one of the most important causes of renovasular hypertension in children in our region.
4. The positive rate of the tuberculin reaction was much higher in children with Takayasu arteritis compared to the general population, and the intensity of the reaction was stronger.
5. Surgical treatment (by-pass operation) showed good results in six out of ten cases.
6. Percutaneous intraluminal angioplasty was very effective for lowering the blood pressure in six out of nine cases. The effect was more prominent in short segmental lesions than in diffuse ones. In three cases, restenosis occurred and longer periods of observation are needed to evalute the long-term results. However, in patients with severe hypertension and intractable congestive heart failure and in an inactive stage, balloon angioplasty may be applied to relieve the hypertension and congestive heart failure. If restenosis occurs, it may be repeated or by-pass surgery may be considered.

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