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Takayasu arteritis: follow-up studies for 20 years

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Summary. We reviewed retrospectively 126 (5 male, 121 female) patients suffering from Takayasu arteritis who had been treated in our clinics from 1971 to 1990. The patients' ages ranged from 19 to 80 yrs old (1990) with a mean age of 48.7 ± 11.8 years. HLA typing analysis in 98 patients revealed that 45 patients (47%) were confirmed as carrying the Bw52 antigen, a high result that is statistically significant as compared with that in healthy Japanese. Arteriograms (performed in 75 patients) revealed that 28 patients (37%) were affected in the aorta and its main branches by this disease (type IV by Nasu's classification) and 23 patients (31%) were affected only in the main branches (type I). The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) improved significantly from 2.55 ± 0.28(+) and 57.0 ± 5.69 mm/hr to 0.53 ± 0.12(+) and 31.2 ± 3.45 mm/hr, respectively after treatment including steroid and antiplatelet therapy ($P < 0.01$). Patients with Bw52 exhibited more severe inflammatory conditions than those without Bw52. Lung scintillations performed in 81 patients showed pulmonary arterial lesions in 50 patients (62%). Echocardiograms revealed aortic regurgitation (AR) in 44 patients (35%), with a significant difference noted between the Bw52 positive group and the Bw52 negative group [29/40 (73%) versus 11/47 (23%), respectively, $P < 0.001$]. Patients with Bw52 were prescribed higher doses of steroids ($P < 0.05$) for longer periods ($P < 0.01$) than those without Bw52. Of 11 patients who died during our study period, 7 died of cardiac complications, all of whom were suffering from AR. HLA analysis performed in 6 of these 7 patients revealed that all carried the Bw52 antigen. In conclusion, the retrospective survey revealed that patients carrying the Bw52 antigen showed more severe inflammatory conditions and progressed more rapidly to complications and the fatal morbid condition, as compared with those without Bw52. This suggests the important role of gene disequilibrium with this HLA antigen.

Key words: Takayasu arteritis – HLA Bw52 – Aortic regurgitation – Inflammatory parameters – Causes of death

Introduction

Takayasu arteritis is a chronic arteritis that mainly affects the aorta and its major branches including coronary and pulmonary arteries [1–6]. This inflammatory condition causes either stenosis, occlusion, and/or dilatation of the involved artery [7]. The clinical manifestations vary greatly depending on the affected arteries [1–3, 8–9].

This disease was first described by Takayasu in 1908. Although more than 80 years has passed since then, the etiology of this morbid condition is still unclear and various causative factors have been discussed [7, 8].

In 1978, Numano et al. reported monozygotic twins with Takayasu arteritis [10]. A survey of these twins and their family led to study on HLA antigens and the participation of the genetic factor(s) in the etiology of this morbid condition. Studies of HLA antigens showed a close relationship between the *A24-Bw52-Dw12* haplotype and Takayasu arteritis [11–13]. Comparative studies on Bw52 and Dw12 antigens revealed a closer association of Bw52 with this disease than Dw12 [14–15].

Although many studies on the clinical features have been carried out, there have been few attempts to discuss how Bw52 reflects clinical features. This study documents the clinical features and courses of 126

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patients, who have been treated in our clinics for 20 years, in relation to HLA Bw52.

Materials and methods

The retrospective study included 126 Japanese patients (5 males, 121 females), all of whom had been diagnosed as having Takayasu arteritis by angiography and/or clinical features treated in our clinics between 1971–1990. The mean age of the patients was 48.7 ± 11.8 years, ranging from 19 to 80 years old. The following items were studied focussing on a comparison between patients with and without HLA Bw52.

HLA analysis

HLA typing was performed in 98 patients of the total 126, using methods described before [11–14].

Angiographic studies

Aortic angiography was performed in 75 patients with Takayasu arteritis by inserting an F4 catheter through the femoral or brachial arteries. The patients were classified into four types according to Nasu's classification, as shown in Fig. 1 [7].

Complications

Various complications have been observed in these patients. Pulmonary arterial lesion aortic regurgitation (AR), hypertension, and cerebrovascular disease are frequently encountered, all of which could be caused by Takayasu arteritis. Eighty-one patients were studied by pulmonary scintillation, using 99mTc macroaggregated albumin.

AR was diagnosed by clinical manifestation, Doppler echocardiograms, and/or arteriograms. The arteriograms and/or Doppler echocardiograms were performed on 81 patients.

Blood pressure was measured in all limbs. Hypertension was diagnosed if the blood pressure in unaffected limbs was recorded as more than 150/90 mmHg in the upper and/or 170/100 mmHg in the lower limbs.

Steroid therapy

Steroid therapy is the most popular remedy for vasculitis. In 38 patients who had been treated with steroids for more than 1 year, we studied whether or not there were some differences in dose, period, and effectiveness between 24 patients with and 14 patients without HLA Bw52 antigens. Effectiveness was evaluated by the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Inflammation

To analyze the effect of medical treatment, changes in ESR and CRP were studied before and after treatment with steroids, vasodilators, antiplatelet therapy, antihypertensives, and so on, according to their clinical conditions. The data were obtained as the mean values of two or three measurements before the medical treatment was started, and the therapeutic effects were judged 1 year after treatment.

Causes of death

Eleven patients died during our study period. The causes of death, severity of AR, whether or not they carried Bw52, and other complications were also investigated.

Results

HLA analysis

As shown in Table 1, HLA analysis revealed a significantly higher frequency of Bw52 [45/98 (46%)] in patients with Takayasu arteritis as compared with in healthy Japanese [16/128 (13%)] ($P < 0.001$) The precise data of most patients were already reported [12].

Angiographic findings

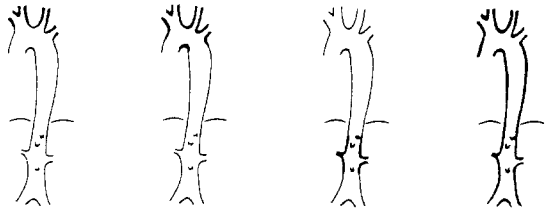
Figure 1 shows the schematic diagrams of the distribution modes of affected lesions in Takayasu arteritis as described by Nasu [7]. Type I involves primarily the aortic branches, type II involves the aortic arch and its branches, type III affects the abdominal aorta and particularly the renal arteries, and type IV combines features of both type II and III.

Angiograms performed on 75 patients revealed type I in 23 patients (31%), type II in 20 patients (27%), type III in 4 patients (5%), and type IV in 28 patients (37%). From these data Japanese patients could be said to belong almost equally to the three groups type I, II, and IV. It should be noticed that a small percent-

Table 1. Association between Bw52 and Takayasu arteritis (TA)

	Bw52(+)	Bw52(−)	Total
Patients	45 (46%)	53 (54%)	98
Healthy Japanese	16 (13%)	112 (87%)	128
Total	61	165	226

Relative risk = 5.94; $\chi^2 = 31.46$; $P < 0.001$
HLA analysis revealed the significantly higher frequency of Bw52 (45/98, 46%) in patients with TA than in healthy Japanese



Type	I	II	III	IV	Total
No.	23	20	4	28	75
%	(31%)	(27%)	(5%)	(37%)	
Bw52(+)	8 (27%)	12 (40%)	1 (3%)	9 (30%)	30
Bw52(−)	10 (33%)	6 (20%)	2 (9%)	12 (40%)	30

Fig. 1. Angiographic findings in 75 patients with Takayasu arteritis (TA)

Table 2. Complications found in patients with Takayasu arteritis

	Total	Bw52(+)	Bw52(−)	Bw52(?)
Pulmonary arterial lesion[a]	50 (62%)	22 (61%)	17 (51%)	10 (67%)
Aortic regurgitation	44 (35%)	29 (66%)*	11 (21%)*	4 (14%)
Angina pectoris	40 (32%)	21 (47%)**	13 (25%)**	6 (21%)
Hypertension	33 (26%)	15 (33%)	15 (28%)	3 (11%)
Renovascular hypertension	4 (3%)	2 (5%)	1 (2%)	1 (3%)
Cerebrovascular disease (excluding TIA)	7 (6%)	2 (5%)	3 (6%)	2 (7%)
Chronic thyroid disease	3 (2%)	1 (2%)	2 (4%)	
Nephrotic syndrome	2 (2%)	2 (5%)		
Autoimmune hepatitis	2 (2%)	1 (2%)		1 (3%)
Chronic glomerulonephritis	1 (1%)			1 (3%)
Sjögren's syndrome	1 (1%)	1 (2%)		
Behçet's disease		1 (1%)	1 (2%)	
Rheumatoid arthritis		1 (1%)		1 (2%)
Bazin's erythema induratum		1 (1%)		1 (2%)
Pyodermia gangrenosum		1 (1%)	1 (2%)	

[a] From 81 patients examined by pulmonary scintillation
* $P < 0.001$; ** $P < 0.05$
Various morbid conditions were found to be complicated in patients with Takayasu arteritis. It should be noticed that patients with Bw52 exhibited a significantly higher frequency of aortic regurgitation and angina pectoris than did those without

age of type III was recorded in Japanese patients. Furthermore among these patients, 30 were confirmed to be carrying HLA Bw52, and the angiograms of these patients revealed type I in 8 patients (27%), type II in 12 patients (40%), type III in 1 patient (3%), and type VI in 9 patients (30%). In 30 patients without Bw52, 10 (33%) patients were type I, 6 (20%) were type II, 2 (7%) were type III, and 12 (40%) were type IV. There was no difference between the Bw52 positive and negative groups in the types of angiogram.

Complications

As shown in Table 2, various morbid conditions were found as complications in patients with Takayasu arteritis. It should be noticed that patients with Bw52 exhibited a statistically significant high frequency of AR and angina pectoris, as compared with patients without this antigen ($P < 0.001$ and $P < 0.05$, respectively). Doppler echocardiograms confirmed AR in 44 patients (35%).

Table 3 revealed the positive correlation between Bw52 and AR ($P < 0.01$): patients carrying the Bw52 antigen had AR complications more frequently than patients without the Bw52 antigen. Pulmonary scintillation studies revealed 50 (62%) patients to be affected in their pulmonary arteries. However, there was no difference between the Bw52 positive and negative groups (Fig. 2).

Table 3. Association between Bw52 and aortic regurgitation (AR) in patients with Takayasu arteritis

	Bw52(+)	Bw52(−)	Total
AR (+)	29 (73%)	11 (23%)	40
AR (−)	11 (27%)	36 (77%)	47
Total	40	47	87

Relative risk = 8.63; $\chi^2 = 21.0$; $P < 0.001$
The Bw52(+) group showed a statistically higher frequency of AR as compared with the Bw52(−) group

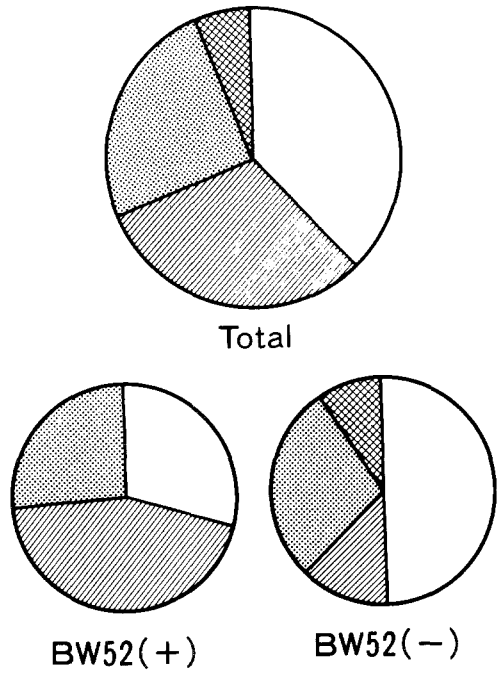


Fig. 2. Findings in pulmonary scintillation in Takayasu arteritis. *White area*, normal; *hatched area*, non-segmental perfusion defect; *dotted area*, segmental perfusion defect; *double hatched area*, lobal perfusion defect

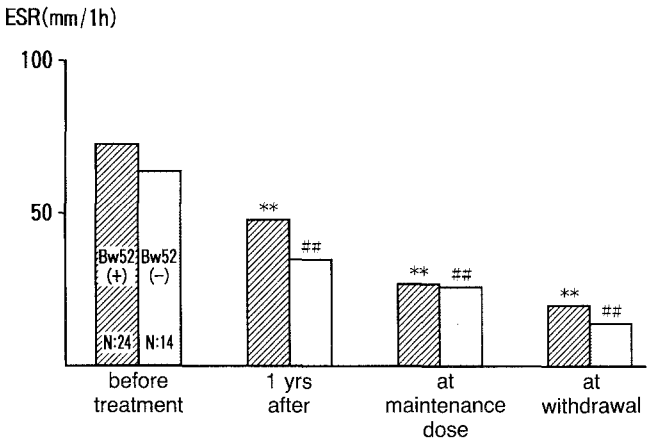


Fig. 3. Changes in erythrocyte sedimentation rate (ESR) with steriod therapy. *Hatched area*, Bw52(+); $^{**}P < 0.01$ before versus after treatment; *white area*, Bw52(−); $^{\#\#}P < 0.01$ before versus after treatment

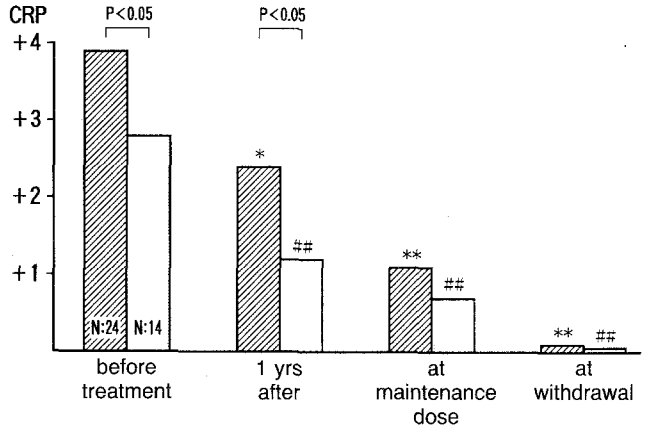


Fig. 4. Changes in C-reactive protein (CRP) with steriod therapy. *Hatched area*, Bw52(+); $^{*}P < 0.05$, $^{**}P < 0.01$ before versus after treatment; *white area*, Bw52(−); $^{\#\#}P < 0.01$ before versus after treatment

Steroid therapy

Table 4 summarizes the dose of steroids initially prescribed (daily dose of prednisolone), the total length of steroid treatment, and how many months were needed to come to the maintenance dose (5–10 mg/day). In this survey "initial dose" means the highest dose prescribed during early treatment in our hospital and "period" expresses the term over which steroids were prescribed continuously or intermittently.

From this data it was confirmed that Bw52 positive patients needed statistically significant high doses of steroids ($P < 0.05$) for much longer periods ($P < 0.01$), as compared with those in Bw52 negative patients. The inflammatory morbid conditions found in Bw52 positive patients were more severe than those in Bw52 negative patients, as characterized by more accentuated ESR and significantly strong reactions of CRP [Figs. 3, 4].

After 1 year's treatment, a higher titer of CRP was still recorded in Bw52 positive patients, in spite of high dose steroid therapy. Comparison of the term required until the maintenance dose was reached revealed an average of 5.7 years in Bw52 positive patients, and 3.7 years in Bw52 negative patients ($P < 0.05$).

Table 4. Steroid therapy for Takayasu arteritis

Treatment Bw52	Initial dose of prednisolon (mg/day)	Term of steroid therapy (years)	Maintenance dose (mg/day)	Term come to maintenance dose (years)
(+) $n = 24$	20.0 ± 1.3	13.7 ± 1.3	5.5 ± 0.3	5.7 ± 0.9
(−) $n = 14$	14.6 ± 1.2	9.4 ± 2.0	4.4 ± 0.4	3.7 ± 1.5
Bw52(+) versus Bw52(−)	$P < 0.05$	$P < 0.01$	–	$P < 0.05$

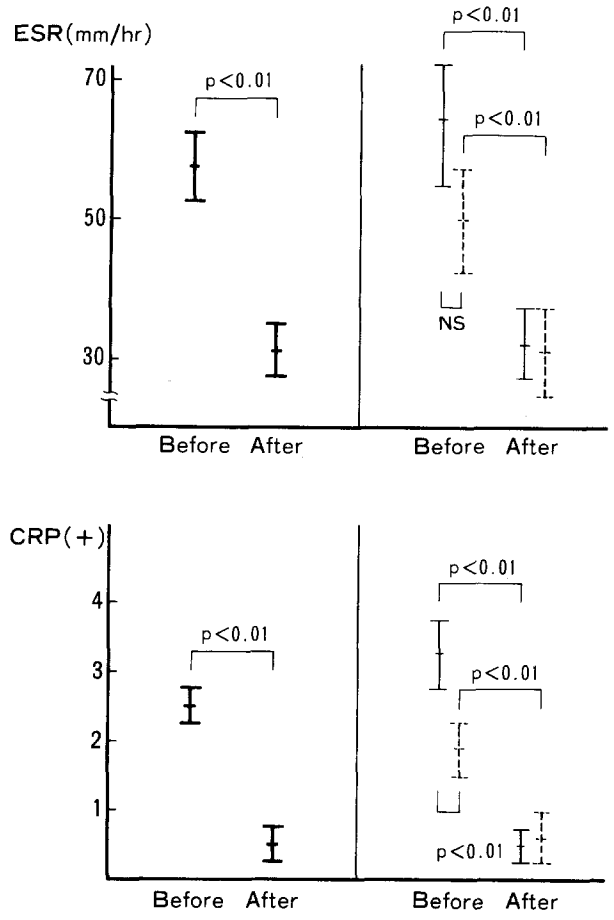


Fig. 5. Changes in ESR and CRP after treatment. Bw52(+) patients exhibited more accentuated ESR and positive CRP than Bw52(−) patients. Antiplatelet and/or steroid therapy were prescribed, and ESR and CRP improved after medical treatment significantly. *Thick solid line*, total; *thin solid* line, Bw52(+); *dashed line*, Bw52(−)

Table 5. Changes in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in patients with Takayasu arteritis before and after medical treatment

		Before	After
ESR	Total	57.0 ± 5.56	31.2 ± 3.45
(mm/hr)	Bw52 (+)	65.5 ± 9.23	32.7 ± 4.63
	Bw52 (−)	49.1 ± 7.64	31.6 ± 5.53
CRP (+)	Total	2.55 ± 0.28	0.53 ± 0.12
	Bw52 (+)	3.32 ± 0.45	0.48 ± 0.16
	Bw52 (−)	1.83 ± 0.33	0.61 ± 0.19

All these data suggest patients carrying HLA Bw52 antigens were affected more severely and showed a resistance to steroid therapy, as compared with Bw52 negative patients.

Inflammatory condition

Table 5 and Fig. 5 show the changes in ESR and CRP in patients with Takayasu arteritis before and after medical treatment, including steroids and others. The Bw52 positive group exhibited significantly higher CRP titers than those in the negative group before medical treatment ($P < 0.01$).

Antiplatelet therapy and/or steroid and sometimes progestrone therapy were the main treatment in our clinics for these patients. By these treatments ESR and CRP improved significantly in both groups 1 year after treatment ($P < 0.01$ and $P < 0.01$, respectively).

Figures 6, 7, 8 summarize the effect in 68 patients of a small dose of aspirin, the basic antiplatelet therapy against platelet aggregation. Patients who underwent combined treatment with other antiplatelet therapies

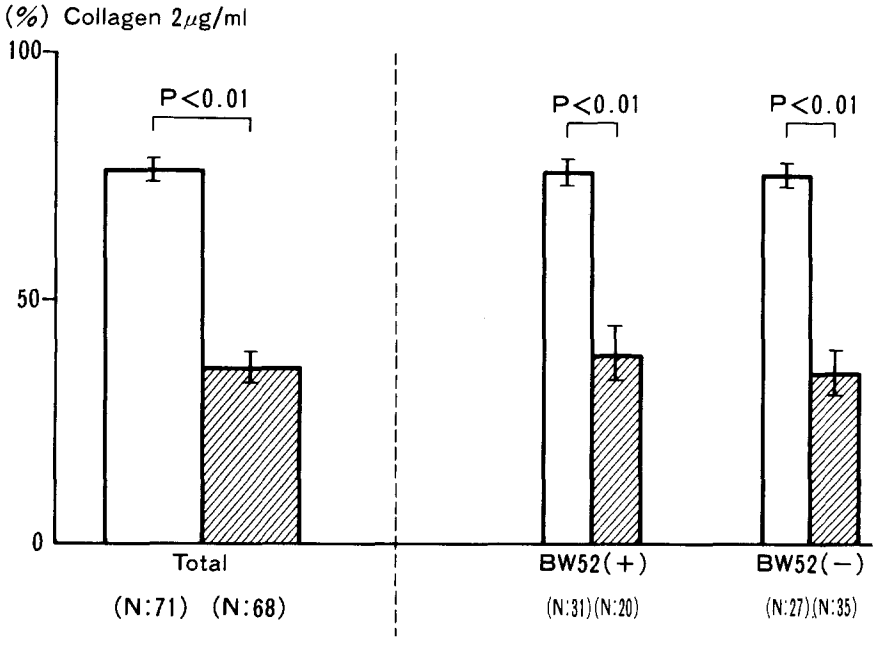


Fig. 6. The effect of aspirin treatment (80 mg/day) on collagen-induced platelet aggregation in patients with Takayasu arteritis. *White area*, before treatment; *hatched area*, after treatment

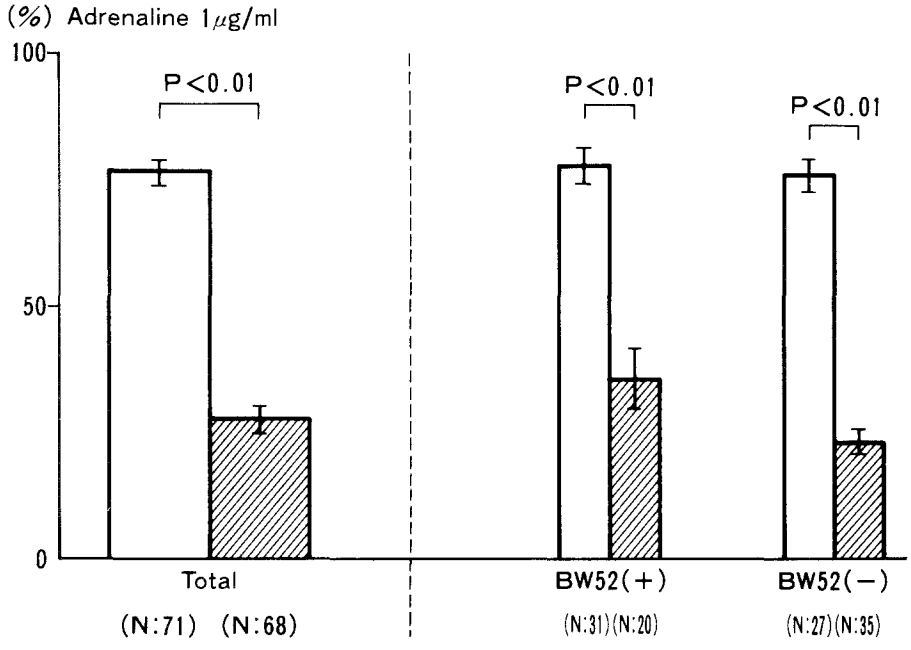


Fig. 7. The effect of aspirin treatment (80 mg/day) on adrenaline-induced platelet aggregration in patients with Takayasu arteritis. *White area*, before treatment; *hatched area*, after treatment

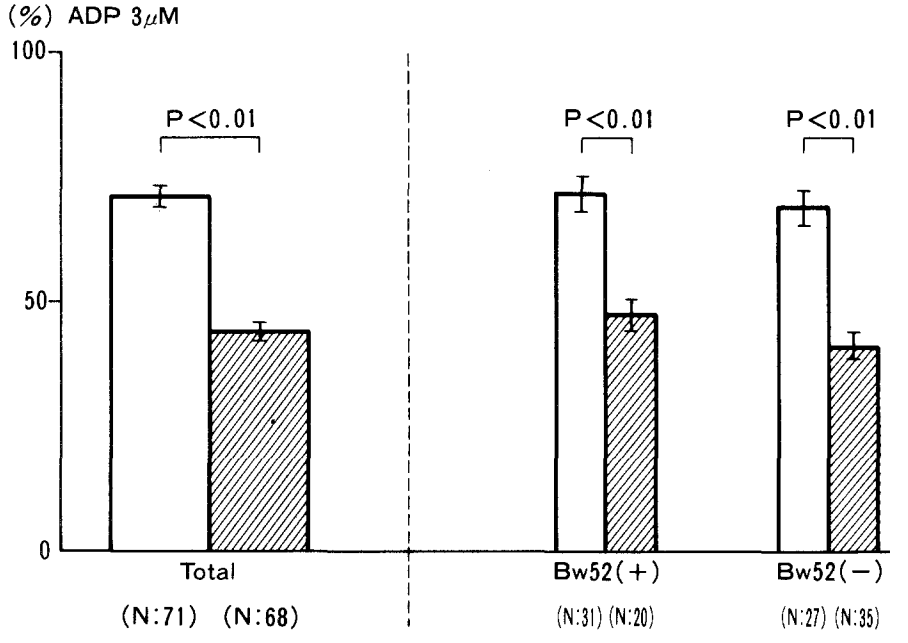


Fig. 8. The effect of aspirin treatment (80 mg/day) on ADP-induced platelet aggregation in patients with Takayasu arteritis. *White area*, before treatment; *hatched area*, after treatment

for short periods and/or steroid therapy were also included in this analysis. A statistically significant improvement of ADP was seen, and adrenaline- and collagen-induced platelet aggregation were confirmed by these treatments. Both the Bw52 positive and negative groups responded equally to antiplatelet therapy. Thus our treatment for Takayasu arteritis is based on the control of platelet aggregration by anti-platelet therapy, control of inflammation by steroids and/or other anti-inflammatory agents, and control of hyperestrogenism by progesterone treatment.

Causes of death

Eleven patients with Takayasu arteritis died during our study period. The causes of death are shown in Table 6: 1 patient died of gastric cancer, 1 of viral encephalitis, and 2 of cerebrovascular disease. The remaining 7 out of the 11 patients, however, died of cardiac disease (3 of congestive heart failure due to severe AR and 4 of sudden cardiac death, probably due to arrhythmia). It should be noticed that all of these 7 suffered from AR. HLA typing performed in

Table 6. Causes of death in 11 patients with Takayasu arteritis

No.	Sex	Age	Cause of death	AR	Bw52	Complications
1	F	36	Congestive heart failure	(╫)	(+)	AP, HT
2	M	40	Congestive heart failure	(+)	(+)	
3	M	42	Congestive heart failure	(╫)	(+)	HT
4	F	48	Sudden death-arrhythmia	(╫)	(+)	CHF, AP, HT
5	F	52	Sudden death-arrhythmia	(+)	(?)	OMI, AVR
6	F	44	Sudden death-arrhythmia (?)	(╫)	(+)	CHF, NS
7	F	54	Sudden death-arrhythmia (?)	(╫)	(+)	CHF, HT, AP, NS
8	F	64	Cerebrovascular disease	(−)	(+)	
9	F	41	Cerebrovascular disease	(−)	(+)	HT
10	F	?	Viral encephalitis	(?)	(?)	CVD
11	F	45	Stomach cancer	(?)	(?)	

AR, aortic regurgitation; *HT*, hypertension; *AP*, angina pectoris; *CHF*, congestive heart failure; *OMI*, old myocardial infarction; *AVR*, aortic valve replacement; *NS*, nephrotic syndrome; *CVD*, cerebrovascular disease
Of 11 patients, 7 died of cardiac disease. It should be noted that all of these 7 patients were suffered from AR and carrying Bw52. Two patients died of CVD

6 of these 7 patients confirmed them as carrying HLA-Bw52.

Discussion

In this retrospective survery we are again impressed by the role of genetic factor(s) in the pathophysiological condition of Takayasu arteritis. The clinical features of patients carrying the Bw52 antigen include severe inflammatory conditions, and more rapid progression to the complicatious of AR, angina pectoris, and congestive heart failure, as compared with those patients without Bw52 [15]. The survery on steroid treatment also suggested the important role of genetic factor(s) by showing that patients with the Bw52 antigen need longer treatment than those without Bw52. In fact patients who showed resistance to steroid therapy were found to be mostly carrying HLA Bw52. Furthermore, it should be emphasized that of the patients that could be checked, almost all who died of cardiac complications of Takayasu's disease were shown to be carrying HLA Bw52. The survey clearly shows that we must pay special attention to patients carrying HLA Bw52 with regards cardiac condition, steroid therapy, and its effectiveness.

The previous survey on the causes of death in patients with Takayasu's disease by the research group on Takayasu arteritis in the Department of Education in Japan revealed that most patients died of cerebrovascular disorders [9]. Nowadays early diagnosis and early treatment of Takayasu arteritis in Japan results in the improvement of the death rate and longer life spans. Accordingly the main causative morbid conditions have changed to the cardiac conditions [16–18]. From this point of view, we emphasized the necessity to the HLA survey and thus special care of patients carrying this haplotype in Japan.

At present we have not yet identified the genetic factor(s) associated with this haplotype. It is postulated that the immunoreactive gene is located near the *B* locus in chromosome 6. The characteristic features of autoimmunity found in Takayasu arteritis and the effectiveness of steroid therapy may suggest the important role of the immunoreactive gene in this morbid condition [19]. It is interesting that, as shown in Table 2, patients with Takayasu arteritis and complications of chronic thyroiditis, nephrotic syndrome, autoimmune hepatitis, and Sjögren syndrome were found to be carrying HLA Bw52.

On the other hand, we could not find any characterized difference among the angiographical and pulmonary scintllations findings and/or hypertension. It is generally accepted that Japanese patients with Takayasu arteritis are effected mainly in the aortic arch and/or thoracic aorta; in our survey 95% of patients were affected in the aortic arch and/or its branches, and patients whose angiogram was type III were very few. Our recent collaborative studies with a Korean group demonstrated the high percentage of type III patients and thus the high frequency of renal hypertension [20–21]. These characteristic differences between Japanese and Korean patients could be attributed to the environmental situation and/or genetic differences. This is our next target to be clarified in relation to research into the etiology of this morbid condition.

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