Case reports

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Takayasu's disease in two brothers

Analysis of HLA types

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SUMMARY Recent studies indicate that certain haplotypes of HLA are frequently associated with Takayasu's disease, and that HLA-A and B loci could determine the predisposition to this disease, especially in women. This paper describes two male sibs with Takayasu's disease in whom HLA typing was carried out. In addition, HLA types were determined on A, B, C, and DR loci of all family members. It was found that no haplotypes were shared by the two patients, but that HLA-Bw52, which has been reported to be frequently associated with Takayasu's disease, was found in one of them. The results suggest that the pathogenesis may be multifactorial and not solely linked to HLA.

Takayasu's disease, a non-specific arteritis of the aorta with or without an involvement of its major branches and pulmonary arteries, is relatively common in orientals and rare in occidentals.^{1 2}

The aetiology remains obscure but recent studies suggest that certain haplotypes of HLA-A and B are frequently associated.³⁻⁹

A genetic factor might play an important role in the pathogenesis for the disease displays a strong predilection for women, particularly young women. We report two male sibs who were found to have Takayasu's disease. HLA typing was performed on all of four loci including A, B, C, and DR (serological version of D loci) of all the family members.

Case reports

CASE 1

A 17-year-old boy presented with syncopal attacks on physical exertion and weakness of the left forearm. The radial pulse was noted to be absent for the first time at the age of 9. The tuberculin test had been known to be positive for six years.

Physical examination disclosed a well-nourished and well-developed boy. The left radial pulse was absent. The blood pressure in the right arm was 192/64 mmHg, and in the right and the left thighs 188/88 mmHg and 160/82 mmHg, respectively.

Systolic bruits were heard over the neck, the left subclavicular, the epigastric, and upper to middle paravertebral regions. The heart sounds were normal. The optic fundi showed dilatation and pulsation of the veins, but there were no microaneurysms or haemorrhages.

The erythrocyte sedimentation rate (ESR) was 24 mm in an hour. The C-reactive protein was positive (4 plus). A serological test for syphilis and a test for rheumatoid factor were negative.

A x-ray film of the chest showed no abnormality. An electrocardiogram showed left ventricular hyper-

Fig. 1 (a) Thoracic aortogram of case 1. Note narrowing of the left subclavian artery. (b) Thoracic aortogram of case 2. Note the grossly dilated aortic arch and thoracic aorta. Both carotid arteries show an irregular narrowed lumen. The innominate artery is a little dilated and irregular.

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trophy ($SV_1 + RV_5 = 5.8$ mV, with no ST segment depression).

Aortography disclosed narrowing of the left subclavian artery (Fig. 1a). Pulmonary perfusion scintigraphy using ^{131}I labelled macroaggregates of albumin (^{131}I -MAA) showed a reduction of blood flow in the upper lobe of the right lung.

CASE 2

This was the younger brother of case 1 and was seen four years later. He was 14 years old. Previously healthy he presented with severe neck pain and general malaise. The tuberculin test had been positive for five years.

Physical examination showed a well-nourished and well-developed boy. The radial, brachial, femoral, and popliteal pulses were palpable bilaterally. The blood pressure was 144/60 and 160/54 mmHg in the right and left arms, respectively. Systolic bruits were audible over both subclavicular fossae and along the carotid arteries of both sides. A faint systolic bruit was also heard over epigastrium and around the umbilical area. The heart sounds were normal. The chest was clear to percussion and auscultation. The ocular fundi were normal. The white blood cell count was $11\,300/\text{mm}^3$, the ESR was 100 mm in an hour, and the C-reactive protein positive (5 plus). Serological tests for syphilis and the rheumatoid factor were negative.

An x-ray film of the chest showed no abnormality. An electrocardiogram showed left ventricular hypertrophy ($SV_1 + RV_5 = 9.6$ mV with depressed ST segments). Plasma renin activity was 2.4 ng/ml per h (normal values: $0.55-1.3$).

Aortography showed a grossly dilated aortic arch, and an innominate artery showing slight dilatation and irregularity (Fig. 1b). The left subclavian, and both carotid arteries showed irregular narrowing of the lumen. The abdominal aorta was also shown to have an irregular wall. Both renal arteries were not

significantly involved. Pulmonary perfusion scintigraphy was normal.

HLA TYPING OF FAMILY

Fig. 2 shows the pedigree and the genotypes of the family. The coefficient of inbreeding is $1/32$ as grandparents on the father's side are first cousins. HLA was determined on A, B, C, and DR loci by the standard NIH method. The antisera used were all approved at the 1st to 4th Japanese Regional HLA Workshop, and the 6th and 7th International Histocompatibility Workshop. The haplotypes of case 1 were A9-Bw35-Cw3-DRw4 and A2-Bw15-X-DRw8, and those of case 2 were A9-Bw52-X-DRw2 and A11-Bw54-Cw1-DRw4. C loci of one of two haplotypes of each individual were not identified (marked X).

Discussion

Two male sibs with Takayasu's disease are described, and HLA types of all the family members are presented.

Takayasu's disease is uncommon among male subjects, and the illness in two male sibs has not so far been reported to our knowledge, though 10 familial cases have been published.³

The aetiology of the disease remains obscure. Recent reports of HLA typing have suggested that genetic factors may play an important role.

Some of them reported that HLA-Bw52⁴⁻⁶ and Bw54⁷ were strongly associated with Takayasu's disease. In the present study, the haplotypes of case 1 were A9-Bw35-Cw3-DRw4 and A2-Bw15-X-DRw8, and those of case 2 were A9-Bw52-X-DRw2 and A11-Bw54-Cw1-DRw4. Numano *et al.*⁸ analysed HLA-A and B locus antigens of all family members of six familial cases. They stated that HLA-A9, A10, B5, or Bw40 were associated with Takayasu's disease in a statistically significant manner. In our cases, HLA-A9 and DRw4 were found in the two affected brothers, though no haplotypes were held in common. The association of DRw4 may be of some interest in view of recent reports that the antigen has been found in high frequency in patients with juvenile onset diabetes,⁹ rheumatoid arthritis,^{10,11} and Vogt-Koyanagi-Harada syndrome¹² in Japanese subjects. The reported association of such variable HLA antigens with Takayasu's disease and the HLA typing of our patients suggest that the pathogenesis may be multifactorial and not solely linked to HLA.

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Fig. 2 The pedigree and the genotypes of the family.

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