

Immunological Studies in Arteritis of the Aorta and Great Vessels*

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Summary: Sera from 21 patients with arteritis of the aorta and great vessels were studied. The mean level of IgG, IgM, and IgA immunoglobulin was raised. The incidence of rheumatoid and antinuclear factor and antibodies to aorta, liver, and thyroid was not raised.

Introduction

Takayasu's syndrome or pulseless disease is also known as branchial arteritis (Koszewski and Hubbard, 1957), brachiocephalic arteritis (Gibbons and King, 1957), the aortic arch syndrome (Ross and McKusick, 1953), arteritis of the aorta and great vessels (Schrire and Asherson, 1964), and may have several causes. However, in most cases the cause is unknown. The protean nature of the disease, the raised gammaglobulin, the high erythrocyte sedimentation rate, and the occurrence of "rheumatic" manifestations either preceding or accompanying the arteritic phase led Hirsch *et al.* (1964) and Strachan (1964) to suggest that the tissue damage might be due in part to an autoimmune process.

We have investigated sera from eight of the patients reported in our previous series (Schrire and Asherson, 1964) and 13 new patients for immunological abnormalities. The present paper describes the finding of a raised level of IgG, IgM, and IgA immunoglobulin.

Materials and Methods

Measurement of Immunoglobulins.—Immunoglobulins were measured by radial diffusion, using commercially available plates. These were calibrated with Behringwerke reference serum. The *t* test was performed on the measurements of diameter.

Tanned Cell Test for Thyroglobulin.—Burroughs Wellcome formalinized tanned cells coated with thyroglobulin were used.

Complement Fixation Test.—The method used was that of Donelley (see Asherson, 1959). 2MHD₁₀₀ of complement titrated in the presence of antigen was employed. Monkey liver and aorta and Burroughs Wellcome freeze-dried thyroid were used.

Rose-Waaler Reaction.—Burroughs Wellcome rabbit antiserum was employed. The rabbit serum was used at 1/4 of the haemagglutinating dose.

Latex Fixation Test.—See Plotz and Singer (1956). A positive control was included.

Antinuclear Factor Test.—The indirect method was undertaken with snap frozen unfixed rat liver. A positive control was included. Antibodies to monkey aorta were sought with unfixed tissue and tissue fixed in absolute alcohol for 30 minutes or acetone for one minute. In all cases the sera were tested undiluted and patients' and control sera were examined in parallel.

Ouchterlony Plate.—Liver and aorta were homogenized in two volumes of pH 7.2 phosphate-buffered saline and centrifuged at 30,000 *g* for 30 minutes; 0.8% ionagar in phosphate-buffered saline was used, and the plates were incubated for 14 days in the cold.

Nomenclature.—IgG, IgA, and IgM are the terms recommended by the World Health Organization (1964) to replace the old terms 7S gammaglobulin, β_2A , and β_2M macroglobulin.

Results

Serum Immunoglobulins.—There was a statistically significant rise in the serum level of the three major groups of immunoglobulins in the patients with aortitis as compared with the controls. The Table shows that the level of IgG, IgA, and IgM in patients with aortitis were 1,586 (1,260), 396 (275), and 159 (111) mg./100 ml. respectively. The figures for the control patients are shown in parentheses. The rises of the three classes are 26, 43, and 43%. The probability of these findings occurring by chance was <0.02, <0.02, and <0.05 respectively.

Tests for Antibodies

The following tests showed no important difference between the patients with aortitis and the control subjects.

Complement Fixation.—Only one patient gave a titre greater than 8 against monkey liver. Three patients and two controls had titres of 8 against aorta. Three patients and one of the controls had titres against thyroid antigen of 8 or 16.

Haemagglutinating Antibody to Thyroglobulin.—One patient (No. 12) gave a titre of 25, while one control subject (No. 8) gave a titre of 250.

Rose-Waaler and Latex Fixation Test.—No serum in this series showed an unequivocal positive latex fixation test (at a dilution of 1/20) or Rose-Waaler reaction (at a dilution of 1/10). One patient (Case 20) and one control subject (No. 7) agglutinated coated sheep red cells to a titre of 1/20, but there was some agglutination of the uncoated cells. One patient (Case 35) had a titre of 1/320 against sheep red cells.

Fluorescent Antibody Tests.—One patient had a weak positive antinuclear factor test. Two patients and two controls produced immunofluorescent staining of the liver, probably involving the sinusoids. The aorta showed bright blue auto-fluorescence due to the elastic fibres. Staining of the adventitia was seen with all the sera. No significant immunofluorescent staining of the media or intima occurred.

Gel Diffusion.—No definite lines were seen against liver or aorta.

Discussion

These results show that patients with aortitis have a raised level of IgG, IgM, and IgA immunoglobulin as compared

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Level of Immunoglobulins, and Occurrence of Antibodies to Liver, Aorta, Thyroid, and Nuclei in Patients with Aortitis and in Control Subjects

	Case No.	Patients							Subject No.	Controls						
		Immunoglobulin Level (mg./100 ml.)			Complement Fixation Test					Immunoglobulin Level (mg./100 ml.)			Complement Fixation Test			
		IgG	IgM	IgA	A.N.F.	Monkey		Human Thyroid		IgG	IgM	IgA	A.N.F.	Monkey		Human Thyroid
						Liver	Aorta							Liver	Aorta	
Coloured female	2	1,600	168	380.8	†	<4	<4	—	4	1,920	168	328.3	—	4	4	<8
	5	1,280	210	232.2	—	<4	<4	—	7	960	68.3	190.4	—	<4	<4	—
	9	1,480	131.3	352.6	—	<4	<4	—	8	880	84	164.1	—	<4	<4	<8
	13	1,240	100	423	—	<4	<4	—	11	880	140	134.1	—	4	<4	—
	18	1,160	110.5	221.4	—	<4	4	—	17	1,200	79.2	352.6	—	<4	<4	—
	19	2,080	168	560	Weak +	<4	8	8	34	1,420	162.5	136	—	<4	<4	—
	20	2,240	240	280	—	16	8	16	38	1,200	73	334	—	—	—	—
	21	1,680	150	264.4	—	<4	<4	—	Mean	1,208	110.7	234	—	—	—	—
	30	1,880	113.5	297.5	—	<4	8	—								
	35	2,360	60	514.6	—	<4	<4	—								
Mean	1,692	145.1	352.6													
Bantu female	10	1,200	185	101.3	†	<4	<4	—	32	920	131.5	340	—	—	—	8
	24	1,800	311	317.3	—	8	<4	—	22	1,560	168	202.5	—	<4	<4	—
	40	1,560	270	297.5	—	—	—	—	28	1,560	131.3	297.5	—	<4	<4	—
	Mean	1,520	255.7	238.7					Mean	1,347	143.6	280				
Coloured male	1	1,320	190	476	—	<4	<4	—	31	1,320	87.5	216.4	—	<4	4	—
	36	1,680	113.5	732	—	—	—	—	41	1,280	87.5	560	—	—	—	—
	37	1,460	230	476	—	—	—	—	Mean	1,300	87.5	388				
	Mean	1,487	177.6	561.3												
Bantu male	6	1,160	70	328.3	—	4	<4	—	26	1,080	113.5	148.7	†	8	4	—
	27	2,440	100	705.2	—	<4	<4	—	39	1,440	68.3	373.3	—	—	—	—
	Mean	1,800	85	516.7					Mean	1,260	90.9	261				
White female	12	1,320	82.4	595	—	<16	<16	—	25	1,820	79.2	352.6	—	<8	<4	—
	16	1,040	168	396.6	—	<4	<4	—	29	780	168	297.5	—	8	8	—
	23	1,400	150	373.3	—	<4	<4	—	33	1,200	82.4	244	—	—	—	—
	Mean	1,253	133	454.9					Mean	1,266	110	298				
Grand mean	1,585.7	159	396.4						1,260	111	274.8					

The complement fixation results are expressed as the reciprocal of the highest titres giving 2 plus complement fixation. —. Indicates negative results. A.N.F. = Antinuclear factor test. †. These patients showed a reticular pattern in the liver in the immunofluorescent test.

with a control group of patients with functional disorders matched for age, sex, and ethnic group. They did not, however, show a raised incidence of autoantibodies of the organ-specific kind found in the Hashimoto thyroiditis group of diseases or of the non-organ-specific kind found in systemic lupus erythematosus. No antibodies against aorta were found by complement fixation, gel precipitation, or immunofluorescence. This is in keeping with the negative findings of Hirsch *et al.* (1964), Strachan (1964), and Paloheimo *et al.* (1966). However, Ito (1966) in Japan found complement-fixing autoantibodies in 12 out of 14 patients, and Maekawa and Ishikawa (1966) found antibodies against the outer layers of the aorta and pulmonary artery by tanned cell haemagglutination. The indirect antiglobulin consumption test was also positive. The reason for the difference between the Japanese and other series is unknown.

The finding of a raised level of immunoglobulin is in keeping with the observations of Ikeda (1966) and Sano and Aiba (1966). The former authors also found a raised level of alphaglobulins. The raised level of immunoglobulin suggests that these patients are exposed to antigenic stimuli which occur to a lesser extent or not at all in the control subjects. There are four main possibilities: (1) the disease may be due to an infection by a parasite or a micro-organism; (2) the disease may be due to an autoimmune process; (3) the disease may be due to antibody antigen complexes which selectively damage the aorta

because of some other (unknown) agent which also acts on the aorta; (4) the raised level of immunoglobulin may be due to an immune response to damage to the aorta and may throw no light on the cause of the damage.

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