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The Change of the Ground Substance of the Aorta in Syphilitic Aortitis

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Veränderungen der Grundsubstanz bei Aortitis syphilitica

Zusammenfassung. 14 Fälle von Mesaortitis luetica werden auf quantitative und qualitative Änderungen im Mucopolysaccharidbestand untersucht. Die Ergebnisse sind folgende:

1. Der Gehalt an Hyaluronsäure und Heparin-Heparitin nimmt ab, der Gehalt an Chondroitinschwefelsäure zu.

2. Die Mucopolysaccharide in der syphilitischen Aortenwand sind weitgehende depolymerisiert. Das Molekulargewicht gewisser Fraktionen liegt wesentlich tiefer als bei Aortenerkrankungen nicht lutischer Ätiologie.

Die in luischen Aorten gefundenen qualitativen und quantitativen Veränderungen im Mucopolysaccharidbestand sind für die Mesaortitis luetica „spezifisch" und unterscheiden sich eindeutig von denjenigen anderer Aortenkrankheiten.

Summary. The authors reviewed the changes of mucopolysaccharides in 14 cases of syphilitic aortitis. The results are as follows:

1. The hyaluronic acid and heparin-heparitin content decreases and chondroitinsulphate accumulates in the aortic wall.

2. The mucopolysaccharides deposited in the aorta are markedly depolymerised and the molecular weight of certain fractions is considerably lower than in other pathological conditions.

The changes in quantity and polymerism of mucopolysaccharides differ from those observed in other conditions and are "specific" for syphilitic aortitis.

The macroscopic and histological differences between syphilitic aortitis and arteriosclerosis were after others exactly described by Doehle in 1895. In recent decades the histological and histochemical differences have been clarified. Hueck (1938) pointed out that in arteriosclerosis the changes of the ground substance of the aorta develop in the intima, whereas in syphilitic aortitis they develop in the media. Benedict (1931) described the differences in the changes of the aortic valve in syphilitic and rheumatic aortitis. The observations of De Faria (1959) showed that the histochemical changes of the intima are slight or missing and in the media a focal MPS increase occurs which may be demonstrated in areas free from inflammation. The changes may be observed in the ascending as well as in the abdominal aorta. The detailed comparative biochemical studies of Faber (1949, 1952) proved that in syphilitic aortitis the cholesterol, collagen, elastine and sulphopolysaccharide content of the aorta differs significantly from that of the hypertensive, arteriosclerotic and diabetic aorta. According to De Faria (1959) and Pjamcev (1964), in changes of syphilitic aortitis the increase in hyaluronidase-sensitive sulpho-MPS (chondroitinsulphate A, chondroitinsulphate C) dominates and the hyaluronic acid is diminished. In cases of syphilitic joint

diseases we observed a significant decrease of hyaluronic acid in the synovial fluid of the knee joint (1966).

We reviewed our case-material of syphilitic aortitis in experimental series. At present the number of cases of syphilitic aortitis is not high and we hope that it will show a further decrease in the future. After this preliminary note we believe that on the basis of our fourteen cases we might draw certain conclusions.

Material and Method

We studied the aorta of fourteen patients between 62 and 74 years of age. In the history of the deceased an infection acquired 30 to 40 years ago was recorded. All showed intensive sero-positivity. The outstanding feature clinically was the aortic insufficiency, cardiac and circulatory failure. Most patients received 20—30 years before death arseno-benzene, bismuth. Penicillin was administered to some of them shortly before death. In four cases aneurysm was observed on the ascending aorta at autopsy. — The cases were selected according to the established principles. The extraction of MPS was performed with the method of BUDDECKE (1960) and the fractionation according to the method of SCHILLER (1961). The quantity of chondroitinsulphate B is shown in the form of iduronic acid (CHAIN and PFOB, 1962) and that of the other fractions in the form of hexuronic acid (DISCHE, 1947). The molecular weight of the various MPS fractions was determined according to the method of MEYER et al. (1948).

Results

In every case we noted the increase of MPS content. The MPS content of the aorta was considerably higher than in the controls, e.g. in the atherosclerotic, hyperthyreotic or diabetic aortas. Concerning the quantitative value of the MPS content, it was similar to that observed in the case of aneurysma dissecans.

1. The Total Acid MPS. The acid MPS content showed values between 2,064 and 3,094 μg per 100 mg, 2,600 μg on the average. No difference according to sex was noted. In case of aneurysm the MPS content of aorta seemed somewhat higher. The average MPS content in 14 syphilitic aortas was 2,523.9, in aneurysm 2,722 and in without than 2,442.2 μg per 100 mg. The difference of MPS content in undilatated and aneurysmal aortae seemed to be considerable, but owing to the small number of cases the significance was not considered.

2. The Quantity of Acid MPS Fractions. In every case the hyaluronic acid content of the aorta decreased, the values being between 92 and 240 μg per 100 mg. The hyaluronidase-sensitive chondroitinsulphate (chondroitinsulphate A, C) was increased considerably, being between 1,040 and 1,740, 1,420.5 μg per 100 mg on the average. The chondroitinsulphate B content of the aorta showed a similar increase and was two to three times higher than in other conditions. The heparin-heparitin content decreased: it was 150 to 320, 235 μg per 100 mg on the average (Table 1).

3. The Ratio of MPS Fractions. In case of syphilitic aortitis the quantity as well as the ratio of the MPS fractions was changed. The significant predominance of chondroitinsulphate may be observed in the aorta. The proportion of hyaluronidase-sensitive chondroitin sulphuric acid is 56.2 per cent on the average, that of chondroitinsulphate B 28.1 per cent. Comparing with other conditions it is especially the quantity and percentual increase of the latter fraction. The chondroitinsulphate fractions represent 84.3 per cent of the MPS. The most marked decrease may be observed in the quantity and ratio of hyaluronic acid.

Table 1. *The change of the ground substance of the aorta in syphilitic aortitis*

Age and sex	Chondroitinsulphat A + C			Chondroitinsulphat B			Hyaluronic acid			Heparin-Heparitin			Total MPS
	Gamma/ 100 mg	No of disaccharide units	Mol. weight	Gamma/ 100 mg	No of disaccharide units	Mol. weight	Gamma/ 100 mg	No of disaccharide units	Mol. weight	Gamma/ 100 mg	No of disaccharide units	Mol. weight	
67, ♂	1,347	91	43,300	670	98	46,700	92	116	45,900	205	100	41,700	2,314
69, ♂	1,070	124	58,800	940	62	29,200	138	102	40,300	180	101	42,000	2,328
72, ♂	1,420	67	31,600	760	62	29,300	240	80	31,600	180	72	29,800	2,600
67, ♂	1,740	73	34,400	850	65	30,700	184	80	31,600	320	63	26,000	3,094
70, ♀	1,040	79	37,300	542	72	34,000	192	103	40,800	290	80	33,100	2,064
68, ♂	1,385	70	33,000	720	74	34,900	170	103	40,800	290	74	30,900	2,565
64, ♀	1,370	65	30,700	840	73	34,500	115	102	40,400	275	65	27,000	2,600
73, ♂	1,620	72	34,000	580	68	32,100	130	110	43,500	210	68	28,200	2,540
70, ♂	1,480	69	32,600	630	72	34,000	170	106	41,900	275	60	24,800	2,555
74, ♀	1,530	70	33,000	780	74	34,900	105	106	41,900	195	69	28,700	2,610
62, ♀	1,710	65	30,700	630	71	33,500	140	101	40,000	150	64	26,500	2,630
67, ♂	1,380	74	34,900	795	69	32,600	215	98	38,800	240	77	32,000	2,630
65, ♂	1,320	72	34,000	580	73	34,700	170	111	43,900	210	72	29,800	2,280
69, ♀	1,480	76	35,900	630	72	34,000	135	106	41,900	270	77	32,000	2,515
Mean	1,421	76	36,000	711	72	34,100	157	96	40,200	235	74	30,900	2,524
Ratio MPS fractions	56.2%			28.1%			6.22%			9.3%			

The predominance of chondroitinsulphate was more distinct in the aneurysmal aorta than in other cases.

4. The Polymerism of MPS Fractions. The MPS molecules showed a extremely low molecular weight. Heparin-heparitin showed with 60 to 101 the lowest polymerism, consisting of 74 disaccharide units on the average, and accordingly, the molecular weight being between 24,800 and 42,000. In the normal aorta as well as under pathological conditions the polymerism of heparin-heparitin was the lowest of the MPS fractions, but in aortitis we may observe a severe depolymerisation as compared to other conditions. A similarly depolymerisation was noted with chondroitinsulphate: the hyaluronidase-sensitive fractions consisted of 76, the hyaluronidase resistents of 72 disaccharide units on the average. The mean molecular weight of chondroitinsulphate A + C was 36,000, that of chondroitinsulphate B was 34,100. In one case where calcification was noted in the aorta, the polymerism of the chondroitinsulphate A + C exceeded the average (124 disaccharide units) and the molecular weight was 58,800. This phenomenon will be discussed later. We found no relation between the quantity of MPS fractions and polymerism nor a different polymerism in case of aneurysm. The highest polymerism was noted in the molecules of hyaluronic acid with 80 to 116, consisting of 96 disaccharide units on the average and the mean value of the molecular weight was 40,200.

5. The Relation between the Quantitative Change of MPS and other Conditions. The total MPS content of the aortic wall was higher than in the intact aorta, in atherosclerosis, hyperthyreosis or diabetic arteriopathia of patient of similar age. Concerning the quantity of total MPS there was no significant difference between syphilitic aortitis, aneurysma dissecans and arteriopathia hypothyreotica. Analysing the quantity of various fractions it was noted that the hyaluronic acid content was lower in syphilitic aortitis than in other conditions, except aneurysma dissecans. The quantity of chondroitinsulphate B was considerably higher than in other conditions. The quantity of chondroitinsulphate A + C, however, was not significantly higher than in aneurysma dissecans or arteriopathia hypothyreotica, but considerably higher than in arteriosclerosis, arteriopathia diabetica or hyperthyreotica. In syphilitic aortitis the heparin-content was considerably higher but does not show any difference compared with healthy controls, hyperthyreotic arteriopathy, or early arteriosclerosis (Table 2).

6. The Relation between the Polymerism of MPS: Fractions and other Pathological Conditions. From the above it may be seen that the analysis of quantitative differences does not always prove the independent change of the ground substance of the aorta in syphilitic aortitis. This applies primarily to the changes of MPS in aneurysma dissecans and syphilitic aortitis, in which the difference of the heparin-heparitin content only may be demonstrated. The polymeric studies showed that behind the quantitative similarity or difference of MPS there are also considerable qualitative differences. In case of syphilitic aortitis the molecular weight of the aortic MPS fractions is lower than in other pathological conditions. The polymerism of hyaluronic acid, chondroitinsulphate A + C, chondroitinsulphate B does not decrease to such an extent as observed in syphilitic aortitis. The molecular weight of the heparin-heparitin was likewise lower than in most pathological conditions, but for arteriosclerosis the marked

Table 2. *The relation between the quantitative change of MPS in different pathological conditions*

Pathological conditions	No of cases	Age	Total MPS	Chondroitinsulphat A + C		Chondroitinsulphat B		Hyaluronic acid		Heparin-Heparitin	
			Gamma/ 100 mg	Gamma/ 100 mg	Mol. weight	Gamma/ 100 mg	Mol. weight	Gamma/ 100 mg	Mol. weight	Gamma/ 100 mg	Mol. weight
Control	20	60—70	782 ± 109.3	269 ± 58.7	135,000	132 ± 42,3	80,000	191 ± 56.7	95,000	190 ± 54.8	52,000
Arteriosclerosis	100	10—90	1,452 ± 666	689 ± 396	130,000	137 ± 54	120,000	194 ± 251	84,000	432 ± 292	45,000
Hypothyreotica	10	44—77	1,561 ± 217	542 ± 109	198,000	190 ± 51.5	193,000	362 ± 97	173,000	467 ± 194.9	140,000
Hyperthyreosis	15	22—53	788 ± 83.3	476 ± 56,9	61,000	119 ± 28.3	45,000	96 ± 9.7	67,000	97 ± 12.3	120,000
Diabetes	29	54—73	648 ± 60.4	244 ± 32.3	137,000	98 ± 25.3	132,000	220 ± 42.2	55,000	86 ± 17.4	43,000
Aneurysma dissecans	6	51—62	1,962 ± 122	1,478 ± 112	202,000	202 ± 26.6	209,000	103 ± 13.7	402,000	179 ± 15.2	136,000
Arteriopathia steroidica	9	54—70	664 ± 22.4	258 ± 9.1	140,000	103 ± 8.2	128,000	207 ± 15.5	105,000	96 ± 13.9	51,000
Arteriopathia adrenalinis	4	61—67	1,491 ± 31.8	690 ± 35.6	64,000	430 ± 18.1	59,000	261 ± 20.4	56,000	110 ± 12	62,000
Aortitis luetica	14	62—74	2,524 ± 240	1,421 ± 20.4	36,000	711 ± 119.9	34,000	157 ± 42.4	38,000	235 ± 51.7	31,000

depolymerisation of this fraction may be demonstrated — too. In arteriosclerosis we may frequently observe — as in syphilitic aortitis — that heparin has a low molecular weight.

We mentioned already that in one case — aortic calcification — the molecular weight of chondroitinsulphate was considerably higher (124 disaccharide units as compared to the average of 78) compared with other cases. Our present studies indicate that a relation exists between the polymerism of chondroitinsulphate and calcification. At present it is not possible to tell more of this relation, but on several occasions we were able to observe that in the calcified aortic wall the molecular weight of chondroitinsulphate is between 60,000 and 80,000.

We consider the changes of aortic MPS as characteristic of syphilitic aortitis. Although the quantitative differences do not show it in every case, the polymeric studies prove that the changes of the ground substance of the aorta are specific. The histochemical and biochemical similarity of aneurysma dissecans and syphilitic aortitis is only seeming because in the former MPS of high molecular weight and in the latter highly depolymerised MPS is deposited on the aortic wall.

Discussion

The structural change of the ground substance of the aorta, the increase of the MPS content or its decrease, is a wellknown fact. According to BRAUNSTEIN (1960) the polymerism of MPS accumulated in the media is very low. Analysing our experience we may state the following:

1. The MPS content of the aorta is considerably increased not only in the ascending part most involved, but also in other areas of the aorta. Further studies are needed to decide whether the MPS accumulation is localized only on the aorta or may be demonstrated in other blood vessels, as well. The increase of the aortic MPS content is extremely, and a similar increase may be observed only in certain cases (aneurysma dissecans, arteriopathia hypothyreotica), but in most pathological conditions (arteriosclerosis, arteriopathia diabetica, etc.) a similarly high MPS content does not occur.

2. In syphilitic aorta the MPS accumulation develops only through the quantitative increase of certain fractions, while the quantity of other fractions decreases as compared to the controls and other pathological conditions. It is mainly the quantitative decrease of hyaluronic acid that is marked and this decreases not only the trophicity of the wall, but also the hydration. The heparin-heparitin content of the aorta is moderately decreased, but not so significantly as in progressive atherosclerosis. The quantitative increase of chondroitinsulphate — during the decrease of the former fractions — results in a structural change in the MPS of the aortic wall. We do not know exactly how this structural change influences the aorta as an organ, but preliminary data show that this chemical change may play a part in the decreased resistance of the aorta, in the destruction, e.g. imperfect regeneration of the structural elements.

3. We consider the changed polymerism of MPS is most important. In all conditions examined by us the MPS showed a considerable polymerisation and higher molecular weight. While in the healthy the order of magnitude of the molecular weight of MPS fraction is several hundreds of thousands, in syphilitic aortitis it is hardly some tens of thousands. In certain conditions (arteriosclerosis,

arteriopathia hyperthyreotica), we observed moderate or severe depolymerisation only in certain fractions and it was never as considerable as in syphilitic aortitis. Follis (1949) was the first who demonstrated that in the cartilage of the newborn, who died of connatal syphilis, the chondroitinsulphate is strongly depolymerized. Recently we presented our studies concerning the synovial fluid of the knee joint (Józsa and Édes, 1966) and demonstrated that beside the quantity of hyaluronic acid the polymerism significantly decreases in the synovial fluid. In view of our observation that a high-grade depolymerisation is present not only in arthropathia syphilitica, but also in chronic syphilitic aortitis, and as this phenomenon was demonstrated in all cases and in all MPS fraction, we are accepting the opinion of Follis (1949) that the Treponema is producing a certain — at present unknown — enzyme, which causes the decomposition of polysaccharides.

Summarizing our observations we may state that in syphilitic aortitis specific changes of the ground substance of the aortic wall develop, which do not occur in other conditions. The MPS content of the wall increases, the ratio and quantity of fractions changes and the polysaccharides of the aorta show a considerable depolymerisation.

References

Benedict, J.: Histologische Unterschiede der durch Endokarditis und Lues verunstalteten Aortenklappen. Virchows Arch. path. Anat. **281**, 780—792 (1931).

Braunstein, H.: Histochemical study of adult aorta. Arch. Path. **69**, 617—632 (1960).

Buddecke, E.: Darstellung und chemische Zusammensetzung von Mucopolysacchariden der Aorta des Menschen. Hoppe-Seylers Z. physiol. Chem. **318**, 33—55 (1960).

Chain, H., u. H. Pfob: Über Mucopolysaccharide in der normalen Aorta und im Aortentransplantat des Hundes. Virchows Arch. path. Anat. **335**, 240—261 (1962).

Dische, Z.: A new specific color reaction of hexuronic acid. J. biol. Chem. **167**, 189—198 (1947).

Doehle, B.: Über Aortenerkrankung bei Syphilitischen und deren Beziehung zur Aneurysmabildung. Dtsch. Arch. klin. Med. 55—60 (1895).

Faber, M.: The human aorta. Sulfat-containing polyuronides and the deposition of cholesterol. Arch. Path. **48**, 342—350 (1949).

—, and G. Moller-Hou: The human aorta. Collagen and elastin in the normal and hypertensive aorta. Acta path. microbiol. scand. **31**, 377—381 (1952).

Faria, L. J. de: Beitrag zur Histogenese und Ätiologie der Medionecrosis aortae idiopathica mit Berücksichtigung der Rolle der Aortitis syphilitica. Beitr. path. Anat. **121**, 243—258 (1959).

Follis, R. H.: Some histochemical observations on normal and diseased cartilage and bone. Trans. Conf. metabol. Interrel. **1**, 27—32 (1949).

Hueck, W.: Über Arteriosklerose. Münch. med. Wschr. **1** (1938).

Józsa, L., and I. Édes: Investigation upon the hyaluronic acid content of the knee-joint liquid in case of degenerative and inflammatory joint diseases [Ungarisch]. Nemzetközi Sebész Kongresszus Budapest 1966.

Meyer, K. H., G. Noelting et P. Bernfeld: Determination du poids moleculaire de polysaccharides naturales par dosage colorimetrique. Helv. chim. Acta **31**, 103—108 (1948).

Pjamcev, T.: Peculiarities of the morphology of the atherosclerosis of the aorta in syphilitical aortitis (Original russisch, ungarisch transliteriert). Arkh. Pat. **26** (4), 53—56 (1964).

Schiller, S., G. A. Slover, and A. Dorfman: Method for separation of acid mucopolysaccharides: Its application to isolation of heparin from skin of rats. J. biol. Chem. **236**, 983—987 (1961).

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