Coronary artery disease in children

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Summary
In this paper an attempt has been made to correlate the morphological aspects of childhood atherosclerosis. Some of the features described are directly related to atherosclerosis. Some of the other conditions described may be related to the subsequent development of atherosclerosis by damaging the vessel wall and thus stimulating the production of atherosclerosis. In other instances, as in the description of the ultrastructural features of the coronary arteries, the exact role of the changes described still remains to be elucidated.

The treatment of atherosclerosis in adulthood does not get to the root of the problem which is obviously prevention. The latter must of course start at an early age. In order to do this we must understand the aetiology and pathogenesis of atherosclerosis.

It is the purpose in this paper to discuss the morphological features of childhood atherosclerosis. It is hoped that some of the features to be discussed will aid in the better understanding of this condition and thus of its prevention and treatment. The normal development of the coronary arteries and their contribution to the development of atherosclerosis will be briefly reviewed. Next to be considered will be the anatomical features in different ethnic groups and the possible effect of these differences on the prevalences of atherosclerosis.

The ultrastructural features of the coronary microcirculation will then be briefly described and an attempt made to relate these features to subsequent pathological findings. Next, the effect of congenital heart lesions—especially those producing coronary hypertension—on the development of atherosclerosis will be considered. The coronary arterial changes in metabolic disorders will also be dealt with briefly.

Finally, the end result of coronary artery disease—namely myocardial infarction—in the childhood period will be considered.

Normal coronary arteries

The natural history of the development of coronary heart disease may be divided into three periods (Abramovici and Neufeld, 1965):

(a) Incubation period (ab ova): fetal life, infants, children, young adults.
(b) Latent period: asymptomatic but with pathological changes present.
(c) Clinical period: signs and symptoms present.

The last period is the one with which we are all familiar. In the search for aetiological factors one must start in the infancy period and even back into fetal life. With this in mind the authors developed their studies of the histology of coronary arteries. Two main aspects were considered: the normal child, and the child with congenital heart disease. In the latter, an attempt was made to learn how the structural changes in the coronary arteries develop, particularly in those lesions where coronary artery hypertension exists, because of its possible implications in the development of atherosclerosis. Special emphasis has been placed in the studies on the differences in structural changes of coronary arteries in different ethnic groups.

From the investigations performed up to the present, the histological changes which appear in the coronary arteries during the different stages of development in fetal life as well as after birth, have now been determined (Neufeld and Vlodaver, 1971).

In fetuses, the intima is not developed, and consists of a very thin layer of endothelial cells. Immediately beneath it lies the internal elastic membrane (lamina elastica interna), which separates the intima from the media.

The first visible changes are seen a few days after birth and are localized in the internal elastic membrane, in the form of splitting or fragmentation. In the region of the splitting of the elastic membrane, fibroblasts proliferate (Fig. 1). In the first post-natal month the splitting of the elastic membrane becomes more prominent and the adjacent smooth muscle cells of the media lose their shape and position and show degenerative changes.

Between the fibres of the split internal elastic membrane, smooth muscle cells begin to appear, tending to run in longitudinal direction. In some
FIG. 1. Left coronary artery of a premature female (stillborn). Endothelial cells lie directly on the intact internal elastic membrane. The medial layer is composed of smooth muscle cells arranged in a circular fashion. HE, × 280.

FIG. 2. Left coronary artery of 2-year-old males. (a) Bedouin, (b) Yemenite, (c) Ashkenazy. Note marked difference among the three ethnic groups: mild changes in the Bedouin, somewhat more pronounced in the Yemenite, and a well developed musculo-elastic layer in the Ashkenazy. Elastic tissue stain, × 34.
instances, proliferation and thickening of the intimal layer are present with an increase of mucopolysaccharides under the endothelium.

The number of smooth muscle cells between the elements originating from the splitting of the internal elastic membrane increases and, in addition, fragmented elastic fibrils begin to appear among the ingrowing muscle fibres. As a result of these changes, a new layer, the musculo-elastic layer, is formed between the obvious intima and media.

Differences in the quantity and intensity of the intimal changes between the sexes are found even in early life. These differences are apparent soon after birth, but are more obvious at the end of the first year of life. These alterations in the coronary arterial internal elastic membrane and intimal changes have been considered by some to be the basis for the development of coronary arteriosclerosis; but this theory has not been proved.

It was decided to see whether the structural changes present in the population studied also occurred in other ethnic groups with low prevalence and incidence of coronary heart disease: Yemenite Jews and Bedouin, both groups living in Israel, were studied. It was assumed that if these changes appeared among them, this would then constitute strong evidence against an anatomical basis for development of atherosclerosis. On the other hand, it was felt that if the structural characteristics of these two groups were different from the original one studied, this would not prove, but would lend support to the theory of an anatomical basis underlying the development of coronary atherosclerosis. The histological changes in the coronary arteries in full-term fetuses, infants and children of three ethnic groups in Israel were studied. These were Ashkenazy Jews (European in origin), Yemenite Jews (from the Yemen) and Bedouin.

The Ashkenazy males were found to have more intima and musculo-elastic tissue than the Bedouin or Yemenite males and for the females of their group and in the others. No differences were found between the right and left coronary arteries in any of the ethnic groups. In the Bedouin the initial elastic changes do not become more pronounced with age as they do in other ethnic groups. The intima of the Ashkenazy males develops in an eccentric form and has a richer collagenous tissue component than that of the children of the Yemenite and Bedouin group (Fig. 2).

These differences in the findings between sexes and ethnic groups in children up to ten years of age are consistent with the known differences in the prevalence of coronary arteriosclerosis and atherosclerosis, coronary heart disease and myocardial infarction in the corresponding adult population (Neufeld, 1973).

**Ultrastructure of the microcirculation**

A great deal of literature has appeared on the clinical, pathological, and functional aspects of the main coronary arteries. To the best of the authors' knowledge, there have been no publications on the ultrastructural features of the coronary microcirculation. Sherf et al. (1977) have recently studied this subject.

The features described apply to the findings in adult hearts. As they may play a role in the morphogenesis of atherosclerosis, it is felt appropriate to discuss these features in this presentation. In addition, in the near future a study of the findings in children is to be undertaken. The coronary arterial tree may be divided into three groups:

(a) main coronary arteries;
(b) small coronary arteries;
(c) terminal coronary vascular bed (microcirculation 100 μ–8 μ–100 μ).

Group (c) is here the main concern. The measurements of the various vessels alone, are insufficient to characterize the vessels, and specific features are necessary to aid in identification. In the arterioles, the cells of the endothelium are prolonged as are the nuclei which do not bulge into the lumen. In addition, there are two to three layers of smooth muscle. In the pre-capillary sphincters, the cells of the endothelium are shorter, the nuclei are larger and bulge into the lumen of the vessel. There is a single layer of smooth muscle cells around the endothelium.

The details of other anatomical structures is outside the scope of this paper. In this study, however, of note is the fact that the pre-capillary sphincter was demonstrated 'on end' as well as on longitudinal sections. This is in contrast to previous studies in which longitudinal demonstrations of the sphincter were made.

Capillary haemodynamics may be regulated by one (or more) of three methods:

(a) periodicity of flow;
(b) unequal duration of flow-time;
(c) lack of relation to systemic pressure.

The capillaries do not control themselves; thus the process which controls the blood flow must be upstream.

Rhodin (1967) was the first to correlate structure with function. He did this by observing the circulation – the smooth blood vessels – in muscle taken from the leg of a rabbit. Rhodin presented only longitudinal sections. In the 'en-face' sections from Sherf's material, open and closed sphincters may be seen. He showed that three or four sphincters are able to control the blood flow in a whole capillary network.
The exact significance of the sphincter mechanism remains to be seen. If, under certain conditions, the sphincters close and remain closed for a varying period of time, the blood supply to an area of the microcirculation may be impaired. Localized ischaemia may be produced. Depending on the number of sphincters and the area involved, the effect on the myocardium will also vary.

Much work still remains to be done in this area. However, the changes outlined hint at a possible role that the microcirculation may play in the development of 'coronary artery disease'.

**Histological changes of the coronary arteries in congenital heart disease**

Histological changes occur in the coronary arteries in several congenital heart lesions; only those in which the coronary arteries are involved in a process resembling atherosclerosis will be discussed. These changes are usually 'secondary' in nature. Secondary changes in the coronary arteries occur when there is hypertension associated with certain congenital cardiovascular anomalies (Neufeld et al., 1962). These changes consist of non-specific intimal changes in the coronary arteries which are thickened. The media of the coronary arteries is also thickened and elastic changes are evident. Such changes are particularly well developed in the following conditions.

**Supravalvular aortic stenosis**

The anomalies causing obstruction to aortic blood flow above the aortic valve are relatively rare and clinically difficult to distinguish from aortic valvular or subvalvular (subaortic) stenosis. They are of three types:

(a) localized zone of obstruction resembling a diaphragm in the ascending aorta;
(b) localized narrowing of the ascending aorta;
(c) uniform narrowing of the entire ascending aorta.

In a post-mortem report of a 2-year-old, the last type was found. The media of the coronary arteries was thickened and deposition of elastic fibres was evident. The changes are attributed to systolic hypertension in the coronary vessels. The proximal segments of the coronary arteries dilate presumably because they fill during ventricular systole and are therefore subjected to the high level of systolic pressure proximal to the obstruction (Ogden, 1970).

**Coarctation of the aorta**

In a histological study of the coronary arteries in hearts of patients in whom coarctation of the aorta was the sole anomaly marked intimal changes and excess collagen tissue were present (Vlodaver and Neufeld, 1968). Atherosclerotic lesions were conspicuous. The media was markedly thickened with rich elastic fibres, interspersed between muscle bundles (Fig. 3). Studies in coarctation of the aorta have shown the left ventricular pressure to be elevated and equal to the pressure in the proximal aorta. Hypertension in the aorta proximal to the coarctation is due not only to the increased resistance but also to the limited capacity and distensibility of the proximal aorta, and the physiological reactions of the left ventricle. Since the coronary arteries originate proximal to the aortic obstruction, elevated pressure in the aorta proximal to the coarctation increases the central coronary perfusing pressure.
Development of coronary hypertension in patients with coarctation of the aorta may well explain the severe changes in the intima in early life and the severe atheroma found in young adults. With coarctation of the aorta, the coronary capacity is larger than normal; this is confirmed by the measurements of the external lumen area, which are larger than those in a control group.

Inherited disorders of metabolism

Inherited disorders of metabolism are genetically determined abnormalities of enzymatic function that result in either an absence or a low concentration of a specific enzyme. The enzymatic deficiency leads to an accumulation of a specific metabolic product proximal to the enzymatic block. The concentration of the product increases in tissues where the metabolic pathway exists, and its accumulation may lead to organ malfunction. Coronary artery involvement has been noted in several of these so-called storage diseases (Blieden and Moller, 1974). In some of these conditions the findings are identical with those in typical atherosclerosis. In others, the findings are similar although not identical. In addition, however, the damage to the coronary arteries produced by the storage material may stimulate the production of atherosclerosis.

Mucopolysaccharidoses

The mucopolysaccharidoses are a group of inherited diseases characterized by the abnormal tissue deposition and/or urinary excretion of mucopolysaccharides. Cardiac involvement occurs in six syndromes of mucopolysaccharidosis. In two of these, Hurler’s and Hunter’s syndromes, the coronary arteries are involved.

Myocardial involvement occurs in areas adjacent to blood vessels. Large cells filled with storage material (gargoyle cells) move into these areas, and if extensive, interfere with myocardial contractility. In both these syndromes the major branches of the coronary arteries may be narrowed by intimal plaques composed of deposits of mucopolysaccharide (Fig. 4).

Protein metabolism

Primary hyperoxaluria describes two rare disorders of the metabolism of oxalic acid, each involving excessive synthesis of oxalic acid and following a pattern of autosomal recessive inheritance.

The clinical course is dominated by calcium oxalate accumulation in various tissues. The heart is one of the major sites and the coronary arteries may show calcium oxalate deposits.

Fig. 4. Histological section of a coronary artery in a patient with Hurler’s syndrome. Note the accumulation of ‘storage cells’ in the intima. HE.

Amino acid metabolism

Because homogentisic oxidase is absent in patients with alkaptonuria, homogentisic acid is not metabolized further. The major clinical features reflect the accumulation and urinary excretion of homogentisic acid; dark urine, pigmentation of cartilage and other tissues and arthritis. Myocardial infarction is a common cause of death, and is related to atheromatous plaques, the blue-black pigmentation of these atheromata being a unique feature.

Homocystinuria

An enzymatic defect in the formation of cystathionine from serine and homocysteine results in this condition. The affected individuals show several features similar to Marfan’s syndrome; however, osteoporosis, mental retardation, and thrombotic vascular disease are also present. Extensive changes occur in the media of the coronary arteries, and lead to dilatation and thrombosis. Clinical manifestations include symptoms of coronary occlusion.

Lipid metabolism

Fabry’s disease is caused by a deficiency of ceramide trihexosidase. Ceramide trihexoside accumulates in most organs, primarily in relation to small blood vessels. The endothelial, perithelial and smooth muscle cells of blood vessels are the vascular sites of accumulation. The disease is inherited as a sex-linked recessive trait.
Clinical manifestations of cardiac involvement include anginal chest pain, myocardial infarction, congestive heart failure and cardiac enlargement.

Sandhoff's disease results from deficient activity of hexosaminidase A and B. Clinical features resemble those of Tay–Sachs disease. In two patients recently described (Blieden et al., 1974), the coronary arteries showed areas of lumenal narrowing due to intimal proliferation of fibroblasts, although no areas of myocardial infarction were present.

G_{M1} gangliosidosis is a condition in which G_{M1} ganglioside accumulates mainly in the central nervous system and, less prominently, in the viscera. In one patient, atheromatous plaques, present in the right coronary artery and descending aorta, contained balloon cells of foamy PAS-negative cytoplasm.

Hyperlipoproteinaemia plays a major role in the development of coronary artery disease. Elevation of serum cholesterol is associated with an increased risk of vascular disease. In the past few years the possible role of genetic factors has been receiving increasing attention. Five types of familial hyperlipidaemia in man have been described. Type II is probably transmitted as a single dominant gene, although polygenic inheritance has been proposed as an alternate hypothesis. Type II hyperlipidaemia is probably the most important as far as the paediatrician is concerned because it can be identified in childhood with a prevalence of about 1 : 200 and the disease in the homozygote state is definitely associated with premature coronary heart disease before the age of 20 years. In the heterozygote state it also appears to be associated with premature coronary heart disease in the fourth and fifth decades.

Tangier disease is characterized by deficiency of high-density lipoprotein in plasma, and by storage of cholesterol esters in many tissues. The enzymatic defect has not been defined. Cardiovascular involvement is believed to be related to the deposition of cholesterol esters. Patients with coronary artery disease have been described.

Myocardial infarction and ischaemia

The function of the coronary arteries is to serve as channels of delivery of oxygenated blood to the myocardium. Failure to perform this task adequately results in damage to the cardiac muscle and possible myocardial infarction. The latter entity is not often considered in a discussion of cardiac disease in the paediatric age range. However, since the incidence of myocardial infarction in children is higher than is usually appreciated, a consideration of this condition is appropriate.

Regarding aetiology, failure of the coronary arterial system to supply oxygenated blood to the myocardium may be due to (1) intrinsic coronary artery disease, which in turn may be congenital or acquired (inflammatory, metabolic, traumatic, neoplastic, degenerative) or (2) normal coronary arterial tree with abnormal perfusant (due in some cases to congenital cardiac lesions). Only the first group of conditions will be discussed. It should be emphasized that the conditions described in the first part of this paper including congenital cardiac lesions and the inherited disorders of metabolism, may be associated with the development of myocardial infarction.

Congenital coronary artery disease

Congenital malformations of the coronary arteries which may result in infarction include: anomalous left coronary artery from the pulmonary trunk, single coronary artery, coronary artery aneurysm, short coronary arteries and coronary arteriovenous fistulae. In addition, anomalous coronary arteries may be compromised at the time of surgery, thus leading to infarction.

Acquired conditions

The list of acquired conditions (diseases) of the coronary arteries is long and includes: rheumatic fever, lupus erythematosus, syphilis, polyarteritis nodosa, medial calcification of the coronary arteries, progeria, Friedreich's ataxia, hypertension, miscellaneous other causes. A detailed discussion of these conditions is outside the scope of this paper.

In several of these conditions, the changes are very similar to those in atherosclerosis. Of note is one case of a young woman who suffered from lupus erythematosus and died of myocardial infarction (Blieden, Tsackracklides and Edwards, 1973). At post-mortem, severe atherosclerotic changes were present. There was no evidence of arteritis; also no significant additional factors such as hypertension were present to explain the changes. The possibility exists that arteritis damaged the vessels and stimulated the development of atherosclerosis.

References


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