Idiopathic arterial calcification in infancy

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Bird, T. (1974). *Archives of Disease in Childhood*, 49, 82. **Idiopathic arterial calcification in infancy.** Two cases of idiopathic generalized arterial calcification in infancy are described. The changes in the vessels consist of calcification in relation to the internal elastic lamina, with secondary subintimal proliferation of fibrous tissue and, occasionally, extension into the media. They are usually most marked in the coronary arteries, with resulting myocardial disease, and acute congestive cardiac failure is the most common presentation and cause of death. The histological picture resembles closely the arterial changes that may occur in severe renal disease, hyperparathyroidism, primary bone disease, hypervitaminosis D, and occasional cases of congenital heart disease.

Generalized arterial calcification is rare in infancy and childhood but is probably the most important cause of occlusive arterial disease at this age (Stryker, 1946a). Most of the cases described have shown a deposition of calcium salts in the region of the internal elastic lamina, sometimes extending into the adjacent media, and associated with subintimal fibrous proliferation. The disease is usually widespread throughout the body, with the heart involved in almost every case.

Although Durante is usually credited with the first description in 1899, his case does not appear typical, and that of Bryant and White (1901) seems more like those described later. The majority of cases since that time have been recorded in America and Germany, and among them are reviews of published reports by Baggenstoss and Keith (1941) and Stryker (1946b). In 1954, Cochrane and Bowden reviewed 40 cases of generalized arterial calcification and added another 8.

The earlier reports produced a diffuse and rather confused picture because many of the cases had associated diseases that could have produced metastatic calcification, the most important being primary renal disease. A more extensive review was made by Moran and Becker (1959), who divided the cases into four groups. (1) Metastatic calcification due to renal disease. (2) Arterial calcification associated with congenital heart disease. (3) Calcium deposition due to hypervitaminosis D. (4) An idiopathic group. After describing and excluding the first three groups, they accepted 44

cases of the idiopathic type and added 2 cases of their own, with the third description of the disease occurring in sibs.

Reports of the idiopathic type of arterial calcification have been few in Britain, with single cases reported by Hughes and Perry (1929) and Mant, Trounce, and Vulliamy (1952). Sladden (1952) described 2 cases, and in 1957, Hunt and Leys added 2 cases occurring in sibs separated by 6 years, each being 4 weeks old at the time of death.

Case reports

Case 1. A male infant of 11 months was admitted to hospital in November 1963 with a history of pallor, nasal discharge, and refusal to feed for 3 days. On the day of admission he developed a loose cough, became lethargic, and had two short cyanotic attacks. He was extremely ill, with temperature 39 °C, pulse 170/min, respiratory rate 60/min, and marked lower rib recession. There was diminished air entry in both lungs, with scattered crepitations, and the liver was palpable. He was digitalized, sedated with phenobarbitone, and given intramuscular penicillin and tetracycline. There was little response, so prednisone was also given. His condition worsened after 6 hours, the signs remaining unchanged; his temperature rose to 40.5 °C and he died 7 hours after admission. There was no history of any previous illness requiring medical attention.

Necropsy examination. The body was that of a normally formed, but small, male infant weighing 7 kg, measuring 70 cm in length, and apparently in normal nutrition.

The main changes were in the heart and lungs. The heart was greatly enlarged (Fig. 1), weighing 130 g (normal 60 g), due mainly to dilatation and hypertrophy

FIG. 1.—Case 1. Dilatation and hypertrophy of left ventricle with myocardial fibrosis and endocardial thickening.

of the left ventricle, the wall being 1.1 cm thick. The endocardium of the left ventricle was opaque and irregularly thickened, and the underlying myocardium was pale, with obvious fibrosis in its inner third. The mitral valve had a short thickened posterior cusp, with broad short chordae covered by thickened endocardium. Other valves were normal. The coronary arteries arose normally and were not obviously thickened or tortuous. The lungs were oedematous, and both lower lobes had the appearance of early consolidation. Apart from moderate diffuse cerebral oedema, no other abnormalities were noted.

Microscopical examination. Numerous blocks from the left ventricle of the heart showed large areas of fibrosis, often with calcification in the inner third of the myocardium, the outer two-thirds being normal (Fig. 2). The endocardium was thickened due to an increase of fibrous and elastic tissue, most marked over the worst affected areas of muscle. Medium-sized branches of the coronary arteries showed marked narrowing due to intense subintimal fibrous proliferation and deposition of calcium along the internal elastic lamina. In some arteries the calcific deposit formed almost a complete ring, and involved the inner fibres of the media (Fig. 3). The media was, however, usually not involved by

calcification, though there was moderate round cell infiltration in the adventitia. The main coronary arteries and the smaller arteries deep in the myocardium did not show these changes. No thromboses, recent or old, were seen. Similar lesions were seen in medium-sized arteries in the pancreatic, peria renal, perithyroid region, and mesentery, but none were seen in the kidney and there was no evidence of renal disease apart from an occasional small deposit of calcium in some collecting tubules. Both lungs showed early bronchopneumonia. There were no changes in the large pulmonary arteries, but some medium-sized arteries showed the earliest changes of calcification of the internal elastic lamina with slight subintimal fibrous thickening (Fig. 4). There was no diffuse calcification of alveolar walls such as may be seen in metastatic calcification. No changes were seen in liver, spleen, or brain. The neck tissues had been preserved for other reasons and it was possible to identify four parathyroid glands, all of normal size and showing no abnormality microscopically. Sections of costochondral junctions showed no evidence of bone disease. Blood and CSF were available, and serum calcium was shown to be 9.8 mg/100 ml with a CSF urea level of 35 mg/100 ml.

Case 2. A female infant aged 3 months was admitted in July 1971 with a history of sweating, vomiting, and refusal to feed for a week, followed by a cough in the last 3 days. She had been a term normal delivery, weighing 3.4 kg at birth, and had made normal progress until this illness, weighing 4.7 kg on admission. She was very ill, with temperature 38.5 °C, circumoral cyanosis, respiratory rate 90/min, and heart-apex rate 180/min. There was dullness at the left base and the liver was enlarged. No cardiac murmurs were heard. Chest x-ray showed generalized enlargement of the heart and electrocardiogram showed evidence of left ventricular hypertrophy with possible ischaemic changes. She was digitalized and given antibiotics, but there was no response; the heart rate was always above 160/min and she died 30 hours after admission. A history taken after the necropsy confirmed that there had been no excessive intake of vitamin D supplements.

Necropsy examination. The infant was normally formed and the main changes were in the heart and lungs. The heart was enlarged (Fig. 5) weighing 90 g (normal 35 g) with dilatation and hypertrophy of the left ventricle, the wall being 0.9 cm thick. The endocardium was opaque and slightly thickened, especially over the anterior and septal walls. The inner half of the myocardium was pale, with the appearance of diffuse fibrosis. No congenital abnormalities were found. The lungs showed marked diffuse congestion and oedema but no consolidation or collapse.

Microscopical examination. The heart showed changes very similar to those in Case 1, but with less fibrosis of the myocardium and with no calcification. The coronary arteries showed almost identical changes (Fig. 6), and there was similar involvement of arteries in

FIG. 2.—Case 1. Myocardium of left ventricle showing fibrosis and calcification. (Haematoxylin and eosin. $\times 120$.)

FIG. 3.—Case 1. Coronary artery with subintimal proliferation and ring of calcification along the elastic lamina. (Haematoxylin and eosin. $\times 50$.)

FIG. 4.—Case 1. Pulmonary artery showing calcification of elastic lamina and early subintimal proliferation. (Haematoxylin and eosin. $\times 200$.)

other parts of the body (Fig. 7). No arterial changes were seen in the kidneys and there was no evidence of renal disease. Two parathyroids only were available and appeared normal. Costochondral junctions showed no changes. CSF urea level was 40 mg/100 ml, but serum calcium was not estimated.

Discussion

Most patients have died between the first few days of life and 1 year, the majority dying in the first 6 months. Some infants present with gastrointestinal symptoms, especially vomiting and refusal to feed, but the most common symptoms are respiratory distress, with cyanosis, tachypnoea, and tachycardia, usually in a previously healthy infant. The majority die within hours or days of onset of illness in acute congestive cardiac failure, presumably due to the widespread severe changes in the coronary arteries found in most cases. Moran and Becker (1959) in their review found 5 cases with thrombosis of coronary arteries, 14 with definite myocardial infarction, and 10 with myocardial fibrosis. There is rarely time for investigation in a desperately ill infant. Biochemical tests have been few, but when they have been done serum calcium has always been normal and there has been no evidence of renal failure. ECG reports are uncommon but have given little help in differentiating the condition from

others with similar symptoms and signs, including endocardial fibroelastosis, aberrant left coronary artery arising from the pulmonary artery, cardiac glycogenosis, and interstitial myocarditis. All of these show cardiac enlargement in chest x-rays, often generalized when in failure, and the ECG usually shows only left ventricular hypertrophy, though sometimes with evidence of ischaemia or infarction. Endocardial fibroelastosis is the most common of these conditions, and was indeed the clinical and necropsy diagnosis in the first of the 2 cases described here. These cases, especially Case 1, showed a definite increase of subendocardial fibrous and elastic tissues, as conspicuous as is seen in the more usual endocardial fibroelastosis without vascular changes. The increase was not always directly related to the underlying myocardial fibrosis and calcification. Fulminating neonatal infections and acute adrenal insufficiency may also produce difficulties in diagnosis. Cochrane and Bowden (1954) suggest that soft tissue radiography of the neck and possibly of limbs, might show arterial calcification and be of diagnostic help, and this has been shown in a few cases (Weens and Marin, 1956). The real difficulty lies in being aware of such a condition before one can apply the correct diagnostic tests.

Histological examination throws little light on the

FIG. 5.—Case 2. *Similar appearances of heart to those in Fig. 1.*

cause. The basophilic staining of calcium salts is readily seen in haematoxylin and eosin stains, and can be confirmed by the von Kossa reaction and alizarin red. It can be shown, however, that iron salts and mucopolysaccharides are also present in the zones of calcium deposition. The calcification can be seen at all stages in different arteries and is usually more advanced in the coronary arteries. Fine granular basophilia is seen in or on the internal elastic lamina, affecting first the crests, which then become flattened as the calcium salts increase in thickness and density, often on both sides of the membrane. Small segments are affected first, but in time the lamina may be converted into a calcified ring. From the earliest changes there is evidence of proliferation of subintimal fibrous tissue, usually in relation to the calcium, and this may cause marked narrowing of the lumen. The calcification sometimes extends into the inner layers of the media, which often appear thinned, but the condition is not primarily a medial calcification. Occasionally a granulomatous reaction, with giant cells, is seen in relation to the calcification, and there is often a round cell infiltration in the adventitia. It was probably the latter changes which gave rise to the suggestions of congenital syphilis in many of the early cases reported.

The picture appears to be identical with that seen in other conditions which may sometimes be associated with arterial calcification both in infancy and later life, including severe chronic renal disease,

FIG. 6.—Case 2. *Coronary artery showing irregular calcification. (Haematoxylin and eosin. $\times 50$.)*

FIG. 7.—Case 2. Artery in pancreas showing irregular calcification. (Haematoxylin and eosin. $\times 120$.)

primary hyperparathyroidism, and excess intake of vitamin D. It is also very similar to the changes described as a common finding in the iliac arteries of newborn infants and of children up to the age of 12 years (Meyer and Lind, 1972a). Meyer and Lind emphasized that the calcification is confined primarily to the homogenous internal elastic membrane, showing again the predilection of this structure to calcify, as noted by many German authors in the past (Jores, 1924). Similar changes have also been described by Meyer and Lind (1972b) in the carotid siphon of normal infants and children. In this paper they examined in more detail the possible effects of local factors (tortuosity, pressure, increased cerebral demands) and general factors. They discussed the effects of parathormone and vitamin D, acting either alone in large doses or in combination with local factors in small doses. It is known that small doses may act as 'sensitizers', producing altered tissue reactivity to calcium (calciophylaxis). They cited experimental work (Grasso and Selye, 1962) in calciophylactic rabbits challenged with substances known to interfere with local tissue metabolism, such as ferric oxide saccharate, and stated that this can produce calcium deposition in coronary arteries followed by intimal proliferation and ischaemic changes in the myocardium similar to those seen in infantile arterial calcification. The changes shown and described by

Grasso and Selye are, however, even more widespread with extensive calcification of muscle, myocardium, and kidney, and the picture is more in keeping with Mönckeberg's medial sclerosis and/or atheroma. There is no proof that vitamin D in prophylactic doses can cause arterial calcification, though the possibility may exist. In Britain, during the 1950s, the recommended daily intake of vitamin D for infants was 2000 to 3000 units, at least 5 times the dose in the United States. More than 200 cases of idiopathic hypercalcaemia were reported from 1953 to 1955, but only 10 were recorded in America. The deposition of calcium salts was mainly in the kidneys and in the soft tissues of the body, with a very typical clinical picture. Arteries were rarely affected and then only in the late stages. Few cases of generalized arterial calcification were reported in the 1950s and 1960s, and the picture of idiopathic hypercalcaemia disappeared when recommended vitamin D intake was reduced to 400 units per day.

Other authors have suggested that there may be an embryonal dystrophy, perhaps hereditary, of the elastic fibres making them more sensitive to toxic agents, of which one might be vitamin D. This has been supported by the three reports of the disease occurring in sibs (Menten and Fetterman, 1948; Hunt and Leys, 1957; Moran and Becker, 1959). The similarity of the lesions in conditions where hypercalcaemia is present, and the not infrequent

finding of calcification in the kidneys, seem to favour some abnormality of calcium metabolism. When conditions such as renal disease, hyperparathyroidism, bone disease, and hypervitaminosis D have been excluded, as in the two cases described here, less well-defined conditions such as infection and allergy have been invoked. At the beginning of the century congenital syphilis was often suggested as a cause, but proof was rarely obtained. In the present cases both mothers and Case 1 had negative Wassermann reactions. Beyer *et al.* (1971) have recently described a 3-week-old infant with typical arterial calcification, who had raised levels of all serum immunoglobulins, especially IgM, from which they inferred the possibility of an intrauterine infection. Allergy has never been proven in any case.

Arterial calcification in infants bears no real resemblance to atheroma or Mönckeberg's sclerosis, but it has been said in a number of reports to resemble closely one condition seen in adult life. This is 'isolated calcification of the internal elastic membrane' described by Jores (1924), and is particularly well seen in the pericapsular arteries of the thyroid gland. I have seen this in approximately 10% of cases in a prospective study of

thyroiditis (Fig. 8). In its earliest stages calcification is limited to the internal elastic membrane, but there is often more evidence of calcific plaque formation with extension into the media and much less subintimal fibrous proliferation. This could represent the responses of different age groups. The changes are seen mainly after middle age and never in childhood, are occasionally found in other sites, are not correlated with atheroma in larger arteries, and do not appear to be of clinical significance.

The idiopathic group of arterial calcification in infancy now appears to be larger than all the groups associated with identifiable causes, and yet the causes remain unknown.

It is still an uncommon condition. The two infants reported here are the only cases seen over a period of 15 years, during which time approximately 950 necropsies have been performed on children less than 2 years old, two-thirds of them being neonates. There were 120 children with congenital heart disease, the commonest findings being major abnormalities of the valves, transposition of the great vessels, septal defects, and persistent ductus arteriosus, with or without coarctation of the aorta. Among these were 4 cases of endocardial fibro-

FIG. 8.—Pericapsular artery in thyroid from a man aged 77 years. (Haematoxylin and eosin. $\times 70$.)

elastosis, 2 glycogen storage disease, 1 aberrant left coronary artery arising from the pulmonary artery, and 3 acute myocarditis, 2 due to Cocksackie virus. None of these showed arterial calcification, nor was it seen in 3 children with chronic renal failure and metastatic calcification. It is difficult to see how further progress can be made unless the diagnosis is seriously considered in cases of rapidly developing congestive cardiac failure in infancy, when there may still be time to carry out investigations.

My thanks are due to Dr. R. O. K. Schade for the photography and Miss Sonia Humphries for secretarial assistance.

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