GENERALIZED ARTERIAL CALCIFICATION OF INFANCY

BY

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In some 40 reported cases of arterial calcification of infancy the proved occurrence in siblings has been described once (Menten and Fetterman, 1948). We report a further example of siblings affected by this disease. It has been described in children of either sex from the age of 1 day to 27 months, usually in the first six months of life. The clinical history and post-mortem appearances in most of the reported examples in early infancy are very similar. The children are born to apparently healthy young parents. The pregnancy and birth are normal, and there is no evidence of abnormal consumption by mother or child of poisons or poisonous dosages of calcifying substances. The infant thrives at first, then, after a few hours, or at the most a few days, of acute symptoms, succumbs from cardiac ischaemia. The symptoms are refusal of feeds, painful rapid respiration, abdominal distension, and heart failure. Occasionally, as in the first of our cases, an electrocardiogram may show the picture typical of coronary occlusion.

Although the clinical manifestations are usually attributable to blockage of the coronary arteries, the calcification affects large and medium-sized arteries throughout the body, and hence we have used the term "generalized arterial calcification."

This is not the only cause of cardiac infarction in infancy, but the syndrome forms a well-defined clinical entity.

Case 1

A male child was born on July 11, 1949. The mother was aged 19 and the father 20; both were in good health with no significant medical history. Both were English and not consanguineous. The child was delivered normally in hospital after an uneventful pregnancy and weighed 7 lb. 13 oz. (3.5 kg.) at birth. He cried vigorously. There was difficulty in establishment at the breast owing to retracted nipples, and the infant was therefore bottle-fed (dried milk). The mother noted no disturbance of any kind until four days before readmission to hospital on August 9, 1949, the infant then being 4 weeks old. The first symptom was refusal of food, and this was followed by vomiting and rapid breathing. The family doctor did not think the child was seriously ill until the day of admission, when respiration became much more difficult.

On arrival at hospital the infant was extremely ill, cyanosed, and pale, with a respiration rate approaching 100, temperature 100° F. (37.8° C.), and heart rate 180–200. The liver was enlarged, but there was no oedema. The clinical diagnosis was of acute infection, possibly accompanied by paroxysmal tachycardia. The cardiogram showed inversion of the T waves and elevation of the ST segment, typical of coronary occlusion. The leucocyte count was 7,000, of which 50% were polymorphonuclears. *X*-ray examination of the chest showed some mottling at the bases. Antibiotics and digoxin were prescribed, but the infant died a few hours later.

Case 2

A third child (a girl) was born at home on October 28, 1955, after a normal pregnancy—a second child (a boy) having been born in 1954. Delivery was spontaneous, and the infant appeared healthy. She was breast-fed and showed no signs of illness until 24 hours before admission to hospital on November 26, then being 4 weeks old. The first symptom was refusal of food, and this was followed by vomiting, the passing of two or three loose stools, and rapid grunting respiration. On admission the infant was cyanosed, pale, and collapsed, with a heart rate of 180, enlargement of liver and spleen, and oedema. There were crepitations over both lungs. The infant died within a few hours.

Post-mortem Examination

Both children were well nourished and externally normal. The most outstanding lesion internally was the calcification of the coronary arteries. The first 2–3 cm. stood out hard, white, and tortuous from a faintly mottled pale-red epicardium. The external iliac, femoral, popliteal, axillary, and brachial arteries were rigidly calcified in almost their whole length, but no other calcification was seen with the naked eye. In Case 2 all of the viscera were radiographed after removal, and, besides the sites already mentioned, calcification was obvious in the mesenteric arteries and in the lingual arteries. The heart of the first child was enlarged (40 g.), predominantly by left ventricular thickening, and the myocardium was firm and light red. In Case 2 the heart was of normal size (23 g.) and the anterior wall of the left ventricle was pale and slightly mottled, the pallor being most pronounced in the inner third. The anterior columnae carniae were flattened. In Case 1 the valves were normal, but in Case 2 there were five minute dark flecks on the contact margin of the posterior mitral cusps. Macroscopically the aorta was normal.

The kidneys were normal to the naked eye. The bones and their epiphysial lines in Case 2 showed no abnormality macroscopically or microscopically. Only the upper pair of parathyroid glands were found in Case 2 despite a prolonged naked-eye and microscopical search. The two found were of normal size and microscopically appeared normal by the criteria of Gilmour (1947). The parathyroid glands were not examined in Case 1.

Microscopical Appearances

Arteries.—The vascular changes in both children were in all major respects similar, although there were minor variations in the degree of involvement at different sites. In addition to the arteries in which calcification was visible, either by naked eye or radiologically, smaller arteries, such as the pericapsular vessels of the thyroid and suprarenals, and arteries in the pancreas and thymus, often showed slight degrees of calcification. The relationship of the calcification to elastic tissue emphasized particularly by Stryker (1946) was very obvious. There was a remarkable predilection for the internal elastic lamina. The minimal lesion was a fine incrustation on each side of the elastic strand, and there were all degrees between this and large irregular masses of calcification distorting the media, with great fibrous intimal proliferation even to the extent of completely obliterating the lumen. In most of the large masses fragments and lengths of elastic tissue could be demonstrated with suitable staining. A common finding was straight bars of calcification along the course of the elastic lamina with loss of the characteristic wavy appearance, and a slight degree of intimal thickening. The pulmonary arteries showed calcification in the elastic strands throughout the media, but no large masses and no intimal changes. A few elastic fibres in the media of the aorta were focally encrusted with calcified material. The affected elastic was at varying levels in the thickness of the aortic media, and sections of all parts of the aorta showed the change. There were no changes in the cerebral vessels. Minimal lesions were present

in the common carotid arteries in Case 1. The elastic laminae remote from the areas of calcification appeared normal.

Heart.—The myocardium of the enlarged heart in Case 1 showed slight patchy interstitial fibrosis, most marked in the subendocardial third and in the papillary muscles, and a few small areas of recent muscle necrosis. In Case 2 there was less fibrosis and more extensive recent infarction, mainly in the anterior wall of the left ventricle. The flecks on the mitral valve consisted of fibrin and red cells, and the valve itself was normal.

Kidneys.—There were amorphous masses of calcification in a few scattered glomeruli in both cases. These masses projected inward from Bowman's capsule and distorted the glomerular tuft. In sections stained with periodic-acid-Schiff the calcification was clearly related to the basement membrane of the capsule, which split to enclose it.

No calcification was found histologically in any other sites, including the gastric mucosa, the pulmonary alveolar walls, and the endocardium.

Examination of the Mother and Surviving Sibling.—This was made clinically, radiologically, and electrocardiographically, and no abnormality was detected. Their serum calcium, blood inorganic phosphorus, and plasma cholesterol were normal.

Discussion

The differential diagnosis clinically between the effects of generalized arterial calcification on the heart and the manifestations of such conditions as glycogen-storage disease, interstitial myocarditis, endocardial fibroelastosis, and aberrant coronary arteries may be difficult. It has been suggested by Cochrane and Bowden (1954) that radiography of the neck may show the arterial calcification.

The aetiology of generalized arterial calcification of infancy is unknown. There is a possibly distinct small group of cases in which primary renal disease may have produced metastatic calcification. Hydronephrosis was found in two children (Bryant and White, 1891; Andersen and Schlesinger, 1942) and congenital renal hypoplasia in one (Cochrane and Bowden, 1954).

A congenital abnormality of the arterial wall and an abnormality of calcium metabolism are the most likely alternatives to account for the remaining cases, and in our opinion the latter is the more probable. The possibility of vitamin D overdosage has been excluded in the majority, although the possibility of hypersensitivity to the vitamin cannot be disproved. The parathyroids have been normal in the few cases in which they have been examined, and no lesions have been found in the bones.

The serum calcium level has been estimated in life in only one example of primary arterial calcification without primary renal disease, and was normal—10.8 mg. per 100 ml. (Traisman *et al.*, 1956). This isolated estimation in a single case cannot be regarded as of great significance.

The predilection of the calcification for elastic tissue has been thought to indicate a primary abnormality of this structure (Stryker, 1946); it has been suggested that the calcification of the arteries in the children with primary renal disease was coincidental. However, calcification round elastic laminae has been described in renal rickets (Shelling and Remsen, 1935), and we have observed a similar picture in material from seven young adults with chronic renal disease and metastatic calcification in the collection of the Bernhard Baron Institute of the London Hospital. In four of these a prominent feature was arterial calcification, most commonly in the form of diffuse calcification of the media, but frequently with a narrow darker staining deposition of calcium against the internal elastic lamina. In all seven cases there were fine incrustations and bars of calcification related to the internal elastic laminae in medium and small arteries closely resembling the lesions of generalized arterial calcification of infancy. It appears that in any state of metastatic calcification the arterial elastic laminae are particularly liable to have calcium deposited round them.

The presence of calcification in the kidneys in many examples of arterial calcification of infancy, either in the glomeruli or in the tubules, suggests that the condition may be part of a generalized metastatic calcification rather than a dystrophic one.

Lightwood (1932) reported widespread arterial calcification in a mentally retarded dwarfed child of 26 months with calcification at sites other than the arteries and kidneys, and with increased density of the bones. The serum calcium was 11 mg. and the blood inorganic phosphorus raised to 6.68 mg. per 100 ml. This case may indicate an aetiological connexion of at least some of the cases of generalized arterial calcification with the severe form of infantile hypercalcaemia described by Fanconi and Girardet (1952), Schlesinger *et al.* (1952), and others.

Furthermore, deposition of calcium in relation to "degenerated" elastica in lingual, meningeal, and renal arteries has been described in a child of 26 months with the severe type of infantile hypercalcaemia (Schlesinger *et al.*, 1956, Case 9).

Until some information becomes available on the biochemical changes in life in generalized arterial calcification of infancy, it is unlikely that any more will be known of its aetiology. It appears from Menten and Fetterman's (1946) cases and ours that the condition may have a familial incidence.

Summary

Two cases are reported of sudden death in infancy from general arterial calcification occurring in a family. Little is known of the aetiology of the condition.

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"The Flour (Composition) Regulations, 1956, require that all flour, other than wholemeal, shall contain minimum quantities of certain nutrients, including vitamins B_1 and B_2, and iron and chalk. Some of these nutrients are partly removed during milling operations, and the lower extraction flours now being sold require, in many cases, the artificial addition of such substances in order to bring the total amounts in the flour up to the minimal quantities laid down by the Regulations. The nutrients are added by millers in the form of a so-called 'master mix' containing all of them in such amounts as to ensure that if the level of one of them in the flour is of the correct order the remaining ones will also normally be present in the required quantity. From the analytical point of view it will be therefore usually necessary to determine only the amounts of one or two of the nutrients present, and to assume, fairly justifiably, that if these are found to be in the correct proportions the others will be likewise. Four samples of flour were examined during the quarter as a preliminary trial. Three of them were of incorrect composition."—Report of the Birmingham City Analyst.