The birthweights of the infants with persistent ductus arteriosus were significantly lower than normal (Table). The boys with a ductus had a mean birthweight of 3·1 kg compared with a normal of 3·5 kg (P < 0·00), and the girls with a ductus had a mean birthweight of 2·87 kg compared with 3·34 kg in the normal (P < 0·001).

Discussion

The birthweight of children with transposition of the great arteries is higher than normal. Campbell (1965) found normal birthweights with atrial septal defect and pulmonary stenosis but low birthweights in girls with coarctation and boys with ventricular septal defect. Engle (1954), reviewing 16 children who died with ventricular septal defects in infancy, noted that 14 of them had birthweights of less than 2·5 kg despite the fact that, with one exception, the pregnancies went to term. It is interesting that in 8 out of 9 children who came to necropsy the small muscular pulmonary arteries had retained their 'fetal character'. Catherine Neill (1968) commented that low birthweight with congenital heart disease is unlikely to be due to the cardiac malformation but rather to other factors. Our observation that children with persistent duc tus arteriosus tended to have a low birthweight—at the time when their haemodynamic status is normal—supports this contention.

However, at this stage we cannot say whether the low birthweight is due to some factor which both retards intrauterine growth and causes persistent duc tus arteriosus, or that children who are small-for-dates tend to have a persistent duc tus arteriosus.

Summary

Children with a persistent duc tus arteriosus requiring ligation under 6 months of age show evidence of intrauterine growth retardation. By the time of operation the weight centile of 17 (71%) of 24 such infants had fallen, but 20 (84%) of the 24 gained weight postoperatively. Those who did not do so were either large-for-dates infants growing towards the normal or small-for-dates infants who remained small postoperatively.

We thank Professor J. D. Keith for access to his records, and the United Oxford Hospitals for financing D. P.'s visit to Toronto in 1973.

References


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Case report

A 16-month-old girl presented with pallor and generalized oedema. There was no complaint of pulmonary or bowel symptoms. She was born of a young unmarried mother with no relevant family history on either side. She was apyreal, pale, and there was generalized oedema. Weight and length were on the 10th and 3rd centiles, respectively. Blood pressure was 100/60 mmHg and the heart rate 110/min. There were no signs of cardiac failure.

Hb 10.6 g/dl; normal total and differential white cell count and platelets; ESR 4 mm/h; Thrombostest 24%; electrolytes normal. Blood urea 17 mg/100 ml; albumin 2.2 g/100 ml; globulin 2.2 g/100 ml; immunoglobulins normal; serum calcium 7.6 mg/100 ml; serum inorganic phosphorus 3.7 mg/100 ml; serum alkaline phosphatase 7 units/100 ml; antistreptolysin titre negative; serum cholesterol 100 mg/100 ml; serum folate >10 ng/ml; urine: no albumin.

Sweat test (done twice): sodium 100, 120 mEq/l; chloride 158, 214 mEq/l. Average daily faecal fat excretion 3.35 g; tryptic activity in fresh stool nil. Virus studies showed paired serology all negative. Stool and throat swab: no viruses were grown in tissue culture.

A diagnosis was made of CF of the pancreas with generalized oedema due to hypoalbuminaemia. She was treated with a high protein diet and conventional therapy for CF but died suddenly one month after admission.

Necropsy examination. The body was slightly oedematous. Bronchi contained thin yellow pus. Pericardium was adherent but could be separated with little difficulty from the epicardium. The heart was markedly enlarged due to left ventricular dilatation. Myocardium of the left ventricle including the septum showed irregular scarring, most marked in the midzone of the ventricular wall. Right ventricle was normal. Coronary arteries appeared to be normal. Pancreas showed accentuation of the normal lobular pattern. Liver was enlarged, pale, and fatty. Spleen and kidneys normal.

The heart muscle showed focal lesions scattered throughout the left ventricle. There were necrotic foci infiltrated with scanty mixed inflammatory cells and a proliferation of fibroblasts. These lesions stained negatively with PAS, but positively with Alcian blue at pH 1, indicating abundant acid mucopolysaccharide in the ground substance; some of these foci showed the early appearance of delicate collagen fibres when stained with van Gieson's. In other areas, which were considered to be lesions of longer duration, dense mature collagen fibres were seen. Coronary vessels were normal.

Pancreas showed wide interlobular fibrosis with loss of pancreatic acini and the formation of cystic ducts containing variable amounts of inspissated secretion. Special stains (PAS and Alcian blue) showed abundant amounts of acid mucopolysaccharides in the ground substance. Lungs, no abnormality; liver, gross fatty infiltration; kidneys, no abnormality.

Discussion

The basic defect in CF remains unknown. Johansen, Anderson, and Hadorn (1968) put forward the hypothesis that there is inhibition of fluid movement from extracellular space into the secretory cells throughout the body, and that this barrier to fluid movement leads to viscous and highly concentrated cellular secretions. They postulated that this inhibition of fluid movement could be related to an abnormal distribution of acid mucopolysaccharides in the connective tissue, though they did not in fact show acid mucopolysaccharides. Fibroblast culture studies and chemical estimation of acid mucopolysaccharides, such as uronic acid, in both affected and heterozygous individuals showed that the mucopolysaccharide content of the extracellular matrix was 2–6 times and in the culture medium 3–10 times that of normal controls (Danes, 1969). By using both chemical estimation and staining methods she further showed that fibroblasts synthesized excess mucopolysaccharides which were released into the extracellular space. Oppenheimer and Esterly (1974) in their review of 35 necropsied cases showed mucoid deposits in the media of the pulmonary artery in 12 severe cases and in 3 of these 12 cases mucoid deposits were also found in the media of the aorta. These mucoid deposits were not Schiff-reactive, were metachromatic with toluidine blue, stained with Alcian blue, indicating that they were mucopolysaccharide deposits. The experimental data and observations and the histological findings of our case suggest that in CF there is an abnormal activity of fibroblasts. Myocardial fibrosis as a complication, however, is rare whereas pancreatic fibrosis is common. Why should this be? It may be necessary for the myocardium to be damaged by some type of nonspecific myocarditis which calls forth an inappropriate response from qualitatively abnormal fibroblasts in CF patients. If so, the pathological changes which occur can be diagrammatically represented as follows.

<table>
<thead>
<tr>
<th>Myocarditis (nonspecific)</th>
<th>Cardiac muscle necrosis</th>
<th>Excess acid mucopolysaccharide release from inappropriate stimulation of fibroblasts</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Myocardial fibrosis</td>
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</table>
Short reports

Alternatively, myocardial fibrosis could be a measure of the severity of CF, a concept supported by the observation of Oppenheimer and Esterly (1974) that acid mucopolysaccharide deposits in the media of the pulmonary artery and aorta were found only in severe cases. In our case abundant acid mucopolysaccharide was shown in heart and pancreas. As controls, 2 cases of cyanotic congenital heart disease with myocardial fibrosis and one myocarditis of undetermined origin, have been stained for acid mucopolysaccharide and negligible amounts were found.

The excessive amount of acid mucopolysaccharide in our case might have arisen from excessive production by fibroblasts along the lines of Danes’s (1969) experiment. The presence in the extracellular space of large amounts of acid mucopolysaccharides may possibly be the immediate cause of cardiac muscle cell damage and replacement fibrosis. It also supports the hypothesis of Johansen et al. of an abnormal distribution of acid mucopolysaccharides in the connective tissue in CF. CF may in future be regarded as a genetic acid mucopolysaccharidosis.

Summary

A case of cystic fibrosis with myocardial fibrosis and acid mucopolysaccharide deposits in the myocardium is described. The case supports the theory that cystic fibrosis may be a genetic acid mucopolysaccharidosis.

REFERENCES


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Neonatal thyrotoxicosis is associated with transplacental passage of human thyroid stimulating immunoglobulin (HTSI)

Neonatal thyrotoxicosis accompanying or following maternal thyrotoxicosis was first described by White (1912) and is usually temporary. Mackenzie (1964) presented evidence that the disorder was related to transplacental passage of long-acting thyroid stimulator (LATS), an immunoglobulin-G, but Mahoney et al. (1964) described a case in which LATS was present in the mother but not in the child. Nutt et al. (1974) reported a case in which LATS was not found in mother or baby, but another immunoglobulin, LATS-P (now known as HTSI), was detected in the mother. We report a further case in which HTSI was detected in both maternal and cord blood, and sequential measurements of HTSI have been made in mother and baby. In the management of thyrotoxic pregnancy estimation of HTSI is helpful. A high value in the maternal serum may be an indication for giving propranolol treatment to the baby from birth.

Case reports

Mother. A 27-year-old teacher with an apparently uneventful first pregnancy until referred by her general practitioner at 34 weeks’ gestation because of thyrotoxicosis. Previous health had been good and there was no family history of thyrotoxicosis. She complained of malaise, vomiting, and intermittent weight loss throughout the pregnancy, and also sweating, nervousness, and irritability. On examination the classical features of thyrotoxicosis were apparent with goitre, bruit, exophthalmos, lid lag, tachycardia, sweating, and tremor. Investigations confirmed thyrotoxicosis with serum protein-bound iodine (PBI) > 20 µg/ml (normal 3·0–8·0), T3 (tri-iodothyronine) resin uptake ratio 1·11 (normal range 0·82–1·28). She was treated with carbimazole 10 mg 8-hourly, and propranolol 40 mg 8-hourly. Her symptoms rapidly improved and at 38 weeks’ gestation she was euthyroid, with PBI 8·3 µg/100 ml. She remained on antithyroid drugs after delivery.

Baby. Labour started spontaneously at 39 weeks’ gestation, but delivery was by Haig-Ferguson forceps...
Is cystic fibrosis an acid mucopolysaccharidosis?

R N Mukherji, P H Moss and C K Heffernan

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