CASE REPORTS

VASCULAR ABNORMALITIES FOLLOWING MATERNAL RUBELLA

BY

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Descriptions of the pathology of pulmonary stenosis following maternal rubella are rare, though the gross anatomy of such stenosis is becoming increasingly well appreciated. An association between pulmonary stenosis and patent ductus arteriosus was reported by Heiner and Nadas in 1958. These authors suggested the possible role of maternal rubella in the aetiology of their cases because of the associated extracardiac defects that were present and because of the normal rarity of the combination of pulmonary stenosis with patent ductus. None of the children described in this report came to necropsy. More recently, Rowe (1963) recorded 11 patients with pulmonary artery stenosis following maternal rubella infection. The diagnosis was based on catheterization and angiographic findings and all his patients were living at the time of the report. To date most of the published reports of pulmonary stenosis following maternal rubella have been of clinical and angiographic studies and, until 1963, only one case describing the histology of pulmonary stenosis following maternal rubella had been reported (Franch and Gay, 1963). For this reason, the following case is placed on record, being one (Case 4) of 5 proven cases described by Venables (1965).

Case Report

P.F. was the third-born child; two previous children are alive and well. During the seventh week of pregnancy the mother suffered an attack of clinical rubella with typical rash and post-auricular lymph-node enlargement.

The baby was born prematurely, weighing 1.62 kg., and was slow to breathe. He was found to have a continuous murmur in the pulmonary area that was attributed to a patent ductus arteriosus. By the age of 9 days the murmur had disappeared. He was first admitted to the Royal Children's Hospital, Melbourne, at the age of 3 weeks with an incarcerated right inguinal hernia. This was reduced and the sac ligated, but repair was deferred as the baby's condition was poor. During this admission he was found to have jerky pulses and a continuous murmur in the pulmonary area. He recovered from the operation and, though he was a slow feeder who tired easily, he gained weight slowly until the age of 4 months when he developed measles. He was admitted one week later because of rapid breathing. A fading morbilliform rash was noted; the lung fields were clear. A moderately loud blowing systolic murmur was heard to the left of the sternum, maximal in the second interspace. The pulses were jerky. He was digitalized and slowly improved but on the sixth day after admission he suddenly became cyanosed and dyspnoeic during a feed. He died the following day.

Necropsy

Macroscopic Findings. Relevant macroscopic changes were confined to the cardiovascular and respiratory systems. The heart was slightly enlarged (cardiothoracic ratio 6:11) and both ventricles were hypertrophied (right ventricle 0.5 cm. in thickness, left ventricle 0.9 cm. in thickness). The valves were all of normal appearance and the endocardium of both atria and ventricles appeared normal. The wall of the

FIG. 1.—On the left is a section of the wall of the aorta (a) showing the media and portion of the thickened intima. The elastic tissue is irregular, fragmented and decreased in amount compared with the control (right). (b) (Verhoeff-van Gieson, $\times 295$.)

main pulmonary artery felt thick and just distal to its bifurcation, both right and left pulmonary arteries became narrowed, each measuring 0.25 cm. internal diameter in the fixed perfused specimen. The main pulmonary artery internal diameter was 0.8 cm. Branches of the right and left pulmonary arteries in the lung hila and in the substance of the lungs appeared normal. The *ductus* was patent (internal diameter 0.2 cm.).

The wall of the *aorta* was greatly thickened, particularly in the descending portion where it measured 0.5 cm. The thickening was intimal and the lining of the vessel was raised into longitudinal folds. The *coronary vessels* were thick and opaque, particularly the anterior branch of the left coronary. The *lungs* contained foci of bronchopneumonia throughout both lower lobes.

Histology. Paraffin sections were cut and stained with hæmatoxylin and eosin, periodic acid-Schiff (P.A.S.) Verhoeff-van Gieson, and aldehyde fuchsin (Gomori). In addition, frozen sections were cut from the *aorta* and pulmonary arteries and stained with toluidine blue and cresyl violet.

The Aorta. The intima was greatly thickened by loose fibroblastic tissue that stained slightly basophilic with hæmatoxylin and eosin. It was not metachromatic but stained faintly pink by P.A.S. technique. The thickness of the intima varied along the length of the *aorta* and around the circumference of the vessel, forming up to half of the total thickness of the wall.

The media appeared vacuolated and the elastic fibres were fragmented and decreased in number compared with normal controls (Fig. 1). The adventitia appeared normal.

Coronary vessels and other arteries including the bronchial arteries showed extensive intimal thickening. This was focal in distribution and involved almost every systemic artery examined. The foci of intimal thickening appeared to be localized to areas of deficient elastic tissue in the wall of the artery and almost invariably this involved the internal elastic lamina (Fig. 2). The staining characters of this intimal tissue

FIG. 2.—Three systemic arteries showing patchy deficiency of the internal elastic lamina and overlying intimal proliferation (a) mesenteric, (b) cerebral, and (c) splenic. (Verhoeff-van Gieson. All $\times 203$.)

were similar to those in the aorta. In spite of the intimal thickening of the coronary vessels the myocardium appeared normal.

In the *pulmonary trunk and branches* and the large elastic pulmonary arteries, the intima varied in thickness and cellularity around the circumference from a minimum of one-eighth the thickness of the media to a maximum of one-third. In the case of the right and left pulmonary arteries, this intimal proliferation appeared to be the main cause of the stenosis though both vessels had narrower external diameters than normal, suggesting there was a general hypoplasia of the entire wall. The intimal tissue stained similarly to that in the aorta.

The media was poorly formed and the arrangement of the elastic fibres was irregular (Fig. 3). In places

FIG. 3.—(a) This shows part of the wall of a large elastic pulmonary artery. The intima is thickened (on left) and the elastic fibres of the media are fragmented, irregular, and partly replaced by collagen. On the right (b) is a normal control. (Verhoeff-van Gieson, $\times 290$.)

there were focal areas where the elastic tissue was fragmented and largely lost, being replaced by collagen. At these sites intimal proliferation was maximal.

Ductus Arteriosus. The muscular wall was thin and there was an increased amount of collagen between the smooth muscle cells. Very little elastic tissue was present. No internal elastic lamina could be identified but in its place were a few irregular bundles of fine elastic fibres. In controls of the same age, the wall of the ductus was approximately twice as thick and elastic tissue was well developed. A prominent elastic lamina could be identified.

Bronchopneumonic consolidation of patchy distribution was seen in the respiratory system. There was no evidence of measles pneumonia.

Discussion

There are not many published descriptions of the histology of pulmonary artery stenosis, but in some of these, abnormal elastic tissue and abnormal vascular structure have been commented upon (Franch and Gay, 1963; Orell, Karnell, and Wahlgren, 1960; Rubin and Strauss, 1961; Oppenheimer, 1938). In only one reported case is there a history of maternal rubella in early pregnancy. This is one of the 2 cases described by Franch and Gay (1963), the patient being a 17-year-old boy whose mother had suffered an attack of rubella in the 10th week of pregnancy. This boy had stenosis of the right pulmonary artery and a patent ductus. The right pulmonary artery was thick-walled due to a great increase in thickness of the intima. The media was not described, but in the illustrations appears normal. The other patient these authors recorded was a boy of 5 years in whom the main pulmonary artery and both main branches were stenosed. Histologically there was intimal proliferation in both pulmonary arteries and dilatation of the distal branches. Occasional areas of thinning of the media were noted with fragmentation of elastic fibres. There was no history of rubella.

In the present case, the chief abnormality was a deficiency of elastic tissue within the walls of both pulmonary and systemic arteries, associated with intimal thickening of these vessels. There was close correlation between the sites of deficiency of elastic tissue and of intimal proliferation. This is a well-known phenomenon, clearly seen in other morbid states, for example hypertensive damage to the media of both systemic and pulmonary vessels in which elastic tissue becomes fragmented as the result, presumably, of increased shearing stresses. In this child, intimal proliferation appeared to be an obvious cause of stenosis of small arteries, and in addition was also the main cause of the pulmonary artery stenosis which was associated with elastic tissue deficiency similar to that apparent in the systemic arteries. In the ductus arteriosus (persistent patency of which is the commonest cardiovascular abnormality following maternal rubella (Campbell, 1961)) there was an apparent decrease in both smooth muscle and elastic tissue content compared with controls of the same age.

At the present time the formation of elastic tissue is regarded as a function of cell activity. The reported studies of elastic fibre formation have suggested both a cellular origin of elastic tissue and an intercellular one. The earlier writers (Orsós, 1926; Krompecher, 1928) thought that the fibres were secreted by connective tissue cells of fibroblastic type. Later writers favoured the hypothesis that the fibres formed within intercellular ground substance without the participation of cells. More recently, electron microscope studies seem to have established beyond doubt that elastic tissue fibres form in ground substance in intimate association with the cells of the media (Karrer and Cox, 1960). These cells appear to bear more resemblance to smooth muscle cells than to fibroblasts (Paule, 1963).

The time at which elastic tissue formation begins is somewhat controversial. Frankel *et al.* (1963) were able to demonstrate fine thread-like aldehyde fuchsin-positive fibres in the developing aorta of a 15 mm. crown-rump human embryo (approximately 6.5 weeks) and other authors have reported demonstrating orcein-positive fibres in embryos of similar ages (Lhotka, 1963).

In order to explain the observations made in this case it is necessary to postulate that in some way fibroblastic or myoblastic activity was interfered with so that elastic tissue formation was impaired. Whether this was the result of infection by the rubella virus and if so how the virus brought about

this change is purely speculation. In 1960 Gray made a histological study of six embryos obtained at therapeutic abortion for rubella in the first trimester of pregnancy. On the basis of his findings, he suggested that the virus invaded the developing foetal tissues leading to cell destruction and that this was responsible for the lesions that developed.

The abnormalities that can be produced in the embryo by rubella are apparently unrelated. Deafness is the most common lesion, then congenital heart disease, cataract and mental deficiency, occasionally with microcephaly (Campbell, 1961; Pitt, 1961). Another well-recognized but less easily defined abnormality that these children show is poor physical development. They are often small at birth and show greatly retarded growth rates (Pitt, 1957). It seems conceivable that there may be a common basis for all these apparently disparate features, perhaps mediated through the connective tissues. Apart from the brain, the parenchymal organs rarely appear to be affected in this group of children, most of the abnormalities being in mesenchymal tissues. This suggests the possibility that the virus in some way damages the mesenchymal tissues but evidence for this is scanty. If Gray's hypothesis is correct, it is conceivable that the presence of the virus may, among other things, interfere with the formation of elastic tissue, thus bringing about the changes described in this report.

Summary

The macroscopic and microscopic necropsy findings are described in an infant whose mother developed rubella in the third week of pregnancy.

Partial deficiency of elastic tissue in systemic and pulmonary arteries associated with intimal proliferation were the chief findings.

It is suggested that the rubella virus may have interfered with normal elastic tissue formation.

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References

- Campbell, M. (1961). Place of maternal rubella in the aetiology of congenital heart disease. *Brit. med. J.*, **1**, 691.
- Franch, R. H., and Gay, B. B., Jr. (1963). Congenital stenosis of the pulmonary artery branches. A classification, with post-mortem findings in two cases. *Amer. J. Med.*, **35**, 512.
- Frankel, H. H., Bernick, S., Patek, P. R., Edmondson, H. A., Peters, R. L., and Paule, W. J. (1963). Elastic membranes of the developing human aorta. *Arch. Path.*, **76**, 474.
- Gray, J. E. (1960). Rubella in pregnancy; a report on six embryos. *Brit. med. J.*, **1**, 1388.
- Heiner, D. C., and Nadas, A. S. (1958). Patent ductus arteriosus in association with pulmonic stenosis—a report of six cases with additional non-cardiac congenital anomalies. *Circulation*, **17**, 232.
- Karrer, H. E., and Cox, J. (1960). Electron microscope study of developing chick embryo aorta. *J. Ultrastruct. Res.*, **4**, 420.
- Krompecher, S. (1928). Die Entwicklung der elastischen Elemente der Arterienwand. *Z. Anat. Entwickl.-Gesch.*, **85**, 704.
- Lhotka, J. F. (1963). Polysaccharide localizations in the developing human aorta. *Anat. Rec.*, **145**, 364.
- Oppenheimer, E. H. (1938). Partial atresia of the main branches of the pulmonary artery occurring in infancy and accompanied by calcification of the pulmonary artery and aorta. *Bull. Johns Hopk. Hosp.*, **63**, 261.
- Orell, S. R., Karnell, J., and Wahlgren, F. (1960). Malformation and multiple stenoses of the pulmonary arteries with pulmonary hypertension. *Acta radiol. (Stockh.)*, **54**, 449.
- Orsós, F. (1926). Des Bindegewebsgerüst der Lymphknoten im normalen und pathologischen Zustand. *Beitr. path. Anat.*, **75**, 15.
- Paule, W. J. (1963). Electron microscopy of the newborn rat aorta. *J. Ultrastruct. Res.*, **8**, 219.
- Pitt, D. B. (1957). Congenital malformations and maternal rubella. *Med. J. Aust.*, **1**, 233.
- (1961). Congenital malformations and maternal rubella: progress report. *Med. J. Aust.*, **1**, 881.
- Rowe, R. D. (1963). Maternal rubella and pulmonary artery stenosis. Report of eleven cases. *Pediatrics*, **32**, 180.
- Rubin, E., and Strauss, L. (1961). Occlusive intrapulmonary vascular anomaly in the newborn: a cause of congenital pulmonary hypertension. *Amer. J. Path.*, **39**, 145.
- Venables, A. W. (1965). The syndrome of pulmonary stenosis complicating maternal rubella. *Brit. Heart J.*, **27**, 49.