

# Familial pulmonary veno-occlusive disease: a case report

C. G. VOORDES, J. R. G. KUIPERS, AND J. D. ELEMA

*From the Departments of Pathology and of Paediatrics, Division of Cardiology,  
University Hospital, Groningen, the Netherlands*

**Voordes, C. G., Kuipers, J. R. G., and Elema, J. D. (1977). Thorax, 32, 763-766. Familial pulmonary veno-occlusive disease: a case report.** A case of pulmonary veno-occlusive disease in a male infant who died at the age of 3 months is presented. Both intra- and extrapulmonary veins were involved. Two years earlier a brother had died of the same disease at the age of 8 weeks, but, in that case, the disease was restricted to the intrapulmonary veins. It is suggested that the disease may have been caused by a viral infection, the mother acting as a carrier. The simultaneous occurrence of intra- and extraparenchymal pulmonary vein occlusion indicates that some instances of isolated extraparenchymal pulmonary vein atresia or obstruction may also have been examples of pulmonary veno-occlusive disease.

Pulmonary veno-occlusive disease (PVOD) is a rare and fatal disease of unknown origin, predominantly but not exclusively occurring in children and young adults. Histopathological characteristics of the disease are narrowing or complete obliteration of the pulmonary veins by irregular intimal thickening and thrombosis in the absence of obvious cardiac abnormalities. Signs of inflammation of the vessel wall are generally absent. Patients develop pulmonary hypertension and die with right heart failure. Most cases show only occlusion of the small pulmonary veins and venules, but in some instances there has also been involvement of larger intrapulmonary veins (Heath *et al.*, 1971; Wagenvoort and Wagenvoort, 1974). Familial occurrence has not been described previously, although the family history in a recent case report is suggestive of PVOD in two siblings (Rosenthal *et al.*, 1973).

We present the history of a child with PVOD whose brother had died of the same disease in early infancy (Wagenvoort *et al.*, 1971).

## Case report

The patient, a boy, was the third child of healthy and unrelated parents. Pregnancy and delivery had been uneventful. Birth weight was 4140 g. There was no history of infection or use of drugs during pregnancy.

At the age of 2 weeks the infant developed feeding difficulties, slight cyanosis, and a failure to grow

satisfactorily. On admission he was 45 days old and weighed 4300 g.

The family history revealed that the second child of these parents had died of PVOD at the age of 2 months about two years earlier (Wagenvoort *et al.*, 1971). The first-born child, a boy, is healthy and now 8 years old. Further familial history was negative.

The patient appeared lively but cyanotic and dyspnoeic. There was a right ventricular impulse, femoral and radial pulsations were good, and the liver margin was palpable 1 cm below the costal margin. On auscultation heart sounds were normal and a grade 2 systolic murmur, maximal in the left axilla, was heard.

Six days after admission cardiac catheterisation was done. Oxygen saturations measured in the caval veins, right atrium, right ventricle, pulmonary artery, and left atrium were all abnormally low with a mean of 40% on the right side and 85% in the left atrium. Right ventricular pressure was 95 mmHg systolic, pulmonary artery pressure 78 mmHg systolic and 40 mmHg diastolic, and wedge pressure (in the left lung) 12 mmHg. Attempts to enter pulmonary veins were unsuccessful. There was no indication of shunting between the two circulations.

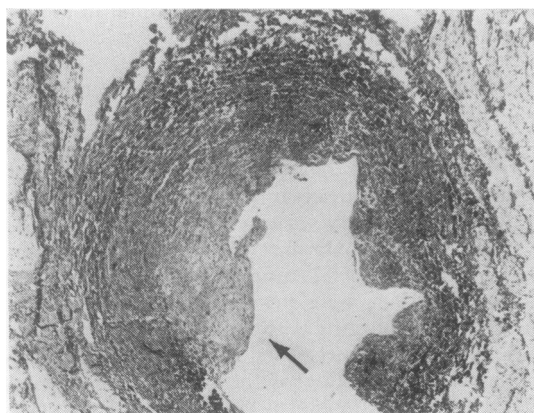
Angiography showed torsion of the left pulmonary artery and poor filling of the upper lobes of both lungs. An open lung biopsy was undertaken to verify the suspicion of PVOD and to evaluate the possibilities of anticoagulant therapy. Six days later the child died after a period in which he was treated with

artificial ventilation and digitalis because of respiratory insufficiency and several episodes of pneumothorax.

#### **PATHOLOGY**

As the histopathology of the lung biopsy specimen was essentially the same as that found in the other lobes at necropsy, the results will be presented together. The pathological findings were confined to the heart and lungs. The heart weighed 40 g and showed right ventricular hypertrophy with a wall thickness of 5 mm. There were no valvular abnormalities and no septal defects. The foramen ovale was patent on probing. There were no thrombi in the heart or in the systemic veins. No gross abnormalities were found in the lungs, pleurae, pleural cavities or pulmonary arteries. The large extrapulmonary veins were more or less stenotic due to a thickening of their walls but their external circumferences were near normal. The vein draining the left upper lobe was completely occluded while the vein from the right upper lobe was stenosed and its tributaries completely occluded. The vein from the right lower lobe was narrow and two of its tributaries were occluded. The vein draining the left lower lobe seemed narrow, but the lumen was open. On further dissection into the lung it was found that all the vein tributaries opened up again but some had a wide, thin-walled lumen.

For microscopy blocks were taken from all lobes and also from the extrapulmonary parts of the veins. All material was fixed in 8% formalin. Microscopy of the extrapulmonary veins showed irregular narrowing of lumina by fibrous intimal thickening (Fig. 1), or even complete obliteration by fibrous tissue penetrated by small capillaries, suggesting



**Fig. 1** *Fibrous intimal thickening (arrow) of the pulmonary vein draining the lower lobe of the right lung. (Haematoxylin and eosin  $\times 60$ .)*

recanalisation of organised thrombi. In one instance fresh thrombotic material adherent to the wall was present (Fig. 2). There was no inflammatory response in the vessel walls. Microscopy of the lung showed scattered haemorrhages and, presumably as a terminal event, bronchopneumonia. Numerous alveolar macrophages were present and the alveolar septa were slightly thickened with oedema and fibroelastic tissue. There was a slight scattered lymphocytic infiltration. The venous channels at all levels showed gross changes with narrowing by irregular fibroelastic intimal thickening and formation of intraluminal fibrotic septa (Figs 3 and 4). Fresh thrombi were found in some small venules. There was no inflammation in the vessel walls. The arteries and arterioles showed considerable medial hypertrophy but no intimal thickening and no thrombi. The lymphatics were considerably widened and



**Fig. 2** *Fresh thrombotic material (arrows) in the vein draining the upper lobe of the right lung. (Elastin  $\times 60$ .)*



**Fig. 3** *Fibrous thickening of the intima in an intrapulmonary vein. (H and E  $\times 130$ .)*

thick-walled. Some contained small fibrinous thrombi.

Microscopy of heart, liver, pancreas, spleen, and kidneys did not reveal any abnormality.

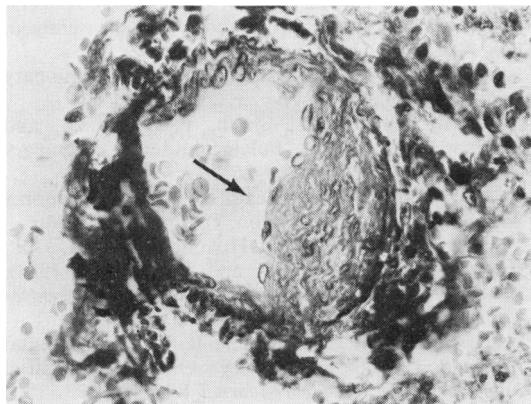


Fig. 4 Small vein with eccentric intimal thickening (arrow) presumed to be of thrombotic origin. (Elastin  $\times 515$ .)

## Discussion

This infant suffered from occlusive disease of intra- and extrapulmonary veins. The microscopic appearance of the lesions and the right ventricular hypertrophy suggested long-standing disease. It is likely that the feeding difficulties, cyanosis, and failure to thrive, first noticed at 2 weeks of age, were related to the development of this disease. An older brother was known to have died from PVOD at the age of 2 months (Wagenvoort *et al.*, 1971).

Similar histopathological changes as in PVOD can be observed in the pulmonary veins in cases of heart disease with chronic pulmonary congestion as in mitral valve disease, aortic atresia, cor triatriatum, and anomalous pulmonary venous drainage (Wagenvoort, 1970). In the absence of extrapulmonary venous obstruction one is dealing by definition with PVOD.

Although the clinical and intrapulmonary pathological findings in our patient are in keeping with a diagnosis of PVOD, by the definition given above the presence of extrapulmonary venous obstruction casts some doubt on this diagnosis. In this respect the patient resembles more those characterised by extrapulmonary venous stenosis, atresia, and thrombosis (Bernstein *et al.*, 1959; Shone *et al.*, 1962; Calderon and Burdine, 1974; Mortensson and Lundström, 1974; Sade *et al.*, 1974).

The relationship between the intra- and extra-

pulmonary vascular changes in this infant is not clear. The intrapulmonary venous changes may have been secondary to obstruction to pulmonary venous outflow caused by the changes in the extrapulmonary veins, but intra- and extrapulmonary disease may also have been an expression of the same process. Although familial occurrence of PVOD has hitherto not been described it appears very unlikely that both infants were suffering from two entirely different and rare diseases that had such a close clinical and pathological likeness. We therefore suggest that this child also died from PVOD. The narrowing of veins, especially the larger extrapulmonary ones, could explain the slightly raised wedge pressure of 12 mmHg. Such an increased wedge pressure was also reported by Heath *et al.* (1971) but in most reported cases it is normal, probably because blood is gradually leaking through partially obstructed veins after the arterial inflow has been interrupted by the catheter (Carrington and Liebow, 1970).

Until now, there has been a suggestion of familial occurrence in only one case of PVOD (Rosenthal *et al.*, 1973). No necropsy was performed on that patient so that confirmation is lacking. The diagnosis of the disease in the patient described by us and in that of his brother (Wagenvoort *et al.*, 1971) seems beyond doubt. The rarity of such familial incidence, however, suggests that genetic factors play a minor role and that, in these two siblings, environmental factors were probably involved.

The presence of fresh thrombi in the pulmonary veins in our patient and the character of the older lesions argue in favour of a thrombotic pathogenesis. The patient of Brown and Harrison (1966), diagnosed histologically as PVOD by means of a lung biopsy, improved considerably on heparin. The aetiology of a thrombotic process restricted to the pulmonary veins remains a matter of speculation. Viruses (British Medical Journal, 1972; Wagenvoort, 1972; Wagenvoort and Wagenvoort, 1974), other infectious agents (Rosenthal *et al.*, 1973), and toxic factors (Wagenvoort, 1972) have been mentioned as possible causes. Substances suspected of causing pulmonary hypertension, such as the appetite-suppressing agent Aminorex (Kay *et al.*, 1971a), or chemicals causing veno-occlusive disease of the liver, like alkaloids of *Crotalaria* and *Senecio* (Kay *et al.*, 1971b), do not affect pulmonary veins. An intrauterine-acquired infection may have caused the disease in the sibling of our own patient (Wagenvoort *et al.*, 1971). Scattered lymphocytic infiltrations, reported in a number of other case histories, suggest the possibility of a primary inflammatory process. In contrast to the findings in the sibling, extrapulmonary manifestations of an inflammatory disease were not found in our case.



The observation of Corrin *et al.* (1974) suggests the possibility of deposition or formation of immune complexes in the venous wall as a pathogenetic mechanism for PVOD. In whatever state the causative agent has been operating in the family under discussion, be it as an infectious or as an antigenic one, it is very likely that the mother acted as a carrier if one assumes that the same agent caused the disease in both children. It is therefore interesting that carrier states are known to exist for HBs-Ag, that this antigen can be vertically transmitted during labour (Schweitzer *et al.*, 1972), and that it may cause vasculitis by an immunological mechanism (Gocke *et al.*, 1970). However, there is no information on the presence of an HBs-Ag-carrier state in the mother, and a recent publication seems to indicate that transfer of HBs-Ag by carriers to their offspring does not occur (Skinhøj *et al.*, 1976).

Any hypothesis about the cause of PVOD in these two siblings remains highly speculative. Although this case report confirms the possibility suggested by the observations of Rosenthal *et al.* (1973) that familial incidence of PVOD may occur, more data are needed to implicate genetic factors, and the possibility remains that an infectious agent is involved.

Apart from the family history there is one other interesting aspect to this case in that both intra- and extrapulmonary veins were involved. There is one recent publication describing occlusion of both intra- and extrapulmonary veins by a process presumably of thrombotic origin (Calderon and Burdine, 1974). This observation suggests that some examples of occlusion restricted to extrapulmonary veins (Bernstein *et al.*, 1959; Shone *et al.*, 1962; Mortenson and Lundström, 1974; Sade *et al.*, 1974) may also have been expressions of pulmonary veno-occlusive disease.

## References

- Bernstein, J., Nolke, A. C., and Reed, J. O. (1959). Extrapulmonic stenosis of the pulmonary veins. *Circulation*, **19**, 891–897.
- British Medical Journal (1972). Pulmonary veno-occlusive disease (Editorial). *British Medical Journal*, **3**, 369.
- Brown, C. H., and Harrison, C. V. (1966). Pulmonary veno-occlusive disease. *Lancet*, **2**, 61–66.
- Calderon, M., and Burdine, A. (1974). Pulmonary veno-occlusive disease. *Journal of Nuclear Medicine*, **15**, 455–457.
- Carrington, C. B., and Liebow, A. A. (1970). Pulmonary veno-occlusive disease. *Human Pathology*, **1**, 322–324.
- Corrin, B., Spencer, H., Turner-Warwick, M., Beales, S. J., and Hamblin, J. J. (1974). Pulmonary veno-occlusion—An immune complex disease? *Virchows Archiv A, Pathological Anatomy and Histology*, **364**, 81–91.
- Gocke, D. J., Morgan, C., Lockshin, M., Hsu, K., Bombardieri, S., and Christian, C. L. (1970). Association between polyarteritis and Australia antigen. *Lancet*, **2**, 1149–1153.
- Heath, D., Scott, O., and Lynch, J. (1971). Pulmonary veno-occlusive disease. *Thorax*, **26**, 663–674.
- Kay, J. M., Heath, D., Smith, P., Bras, G., and Summerell, J. (1971b). Fulvina and the pulmonary circulation. *Thorax*, **26**, 249–261.
- Kay, J. M., Smith, P., and Heath, D. (1971a). Aminorex and the pulmonary circulation. *Thorax*, **26**, 262–270.
- Le Tan Vinh, Tran Van Duc, Huault, G., Gallet, J. P., Joly, C., Aussannaire, M., and Thieffry, S. (1974). La maladie veino-occlusive du poumon. *Archives Françaises de Pédiatrie*, **31**, 187–199.
- Mortenson, W., and Lundström, N. R. (1974). Congenital obstruction of the pulmonary veins at their atrial junctions. *American Heart Journal*, **87**, 359–362.
- Rosenthal, A., Vawter, G., and Wagenvoort, C. A. (1973). Intrapulmonary veno-occlusive disease. *American Journal of Cardiology*, **31**, 78–83.
- Sade, R. M., Freed, M. D., Matthews, E. C., and Castaneda, A. R. (1974). Stenosis of individual pulmonary veins. *Journal of Thoracic and Cardiovascular Surgery*, **67**, 953–962.
- Schweitzer, I. L., Wing, A., McPeak, C., and Spears, R. L. (1972). Hepatitis and hepatitis associated antigen in 56 mother–infant pairs. *Journal of the American Medical Association*, **220**, 1092–1095.
- Shone, J. D., Amplatz, K., Anderson, R. C., Adams, P., Jr., and Edwards, J. E. (1962). Congenital stenosis of individual pulmonary veins. *Circulation*, **26**, 574–581.
- Skinhøj, P., Cohn, J., and Bradburne, A. F. (1976). Transmission of hepatitis type B from healthy HBs-Ag-positive mothers. *British Medical Journal*, **1**, 10–11.
- Wagenvoort, C. A. (1970). Morphologic changes in intrapulmonary veins. *Human Pathology*, **1**, 205–213.
- Wagenvoort, C. A. (1972). Vasoconstrictive primary pulmonary hypertension and pulmonary veno-occlusive disease. *Cardiovascular Clinics*, **4** (2), 97–113.
- Wagenvoort, C. A., Losekoot, G., and Mulder, E. (1971). Pulmonary veno-occlusive disease of presumably intrauterine origin. *Thorax*, **26**, 429–434.
- Wagenvoort, C. A., and Wagenvoort, N. (1974). The pathology of pulmonary veno-occlusive disease. *Virchows Archiv A, Pathological Anatomy and Histology*, **364**, 69–79.

C. G. Voordes, J. R. G. Kuipers, and J. D. Elema

Requests for reprints to: Dr. C. G. Voordes, Department of Pathology, University of Groningen, The Netherlands.