Medical Memoranda

Rubella Syndrome: Escape of a Twin

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The ability of the rubella virus to cause damage to the embryo is not in doubt. There are, however, different views about the degree of risk to the infant when there is exposure to rubella in early pregnancy. Butler *et al.* (1965) suggest that a subclinical infection with seroconversion can occur without clinical defects in the child. To show that this is indeed possible we report the outcome of a twin pregnancy in which a mother had rubella in the early months. One infant is normal but the other severely affected with the classical "rubella syndrome."

Case Report

The patient, a full-term infant (one of a twin pregnancy), was delivered by forceps as a breech after a transverse lie. He was shocked at delivery, but settled down well and thrived. The twins were binovular. The maternal notes reported two separate placentae.

The patient first came to notice at the age of 1 year, when visual disturbance was reported. He was noted to have bilateral cataract with slight buphthalmos on one side and microphthalmos on the other. While he was in hospital for treatment (V. T. L.) it was discovered that he had a congenital heart lesion. He was noted to be much smaller than his twin, and generally retarded in physical and neuromuscular development.

Investigation of his heart (by G. H. W.), including catheterization and angiograms, showed a slight pulmonary valvular stenosis and slight stenosis at the origin of the right pulmonary artery; there was a loud precordial systolic murmur. Further inquiry revealed that the mother had had a mild illness (with a rash) early in pregnancy. The exact date was not recalled, and no diagnosis had been reached or attempted. The suspicion of rubella syndrome was raised, and blood was sent to Dr. J. A. Dudgeon at Great Ormond Street. He reported that the child had a rubella-neutralizing antibody titre of 1/256 and his mother 1/64. This strongly suggested that the mother's illness had indeed been rubella, and that the child was affected with the classical syndrome. Blood from his twin brother was obtained at the age of 22 months. Dr. Dudgeon reported that it showed the same high titre of antibody (1/256). Clinical examination of the twin brother at the age of 3 years revealed a normal child with normal eyes. There was no evidence of any heart lesion and he was developing normally in every way.

The patient remained a retarded little boy with a head circumference well below the 10th percentile (18 in. (46 cm.) at 3 years). There was some early speech retardation, but he has developed clear (but limited) speech. There was no significant detectable deafness.

The pattern of eye, heart, and brain lesions often associated with a small head circumference is familiar in the fully developed rubella syndrome. The history, serology, and clinical findings leave no room for doubt that the patient had had an intrauterine rubella infection.

Comment

The absence of clinical abnormalities and the necessity to seek retrospective evidence of rubella infection in pregnancy would have made it most unlikely that the normal child's blood would have been investigated if it had not been for the existence of his affected twin. There seems no doubt, however, that he *was* infected with the rubella virus at the same time as his mother and twin brother, but that he has escaped damage. This confirms suspicions previously held that there is a good deal of individual variation in the degree of damage to the individual foetus in authentic cases of maternal rubella infection.

We are grateful to Dr. J. A. Dudgeon for permission to publish his results on antibody-neutralization tests.

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Idiopathic Pulmonary Haemosiderosis and Rheumatoid Arthritis

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Idiopathic pulmonary haemosiderosis is characterized by haemoptysis and anaemia due to recurrent intrapulmonary capillary bleeding. The subject has been reviewed by Soergel and Sommers (1962). The aetiology is unknown, though many theories have been advanced. Steiner (1954) and Steiner and Nabrady (1965) have suggested that the disorder has an immuno-allergic basis.

In a disorder of unknown aetiology, where there is suspicion that an immunological mechanism may be involved, the occurrence in the same patient of other diseases in which an immunological defect is commonly assumed is of interest. This report concerns a patient with idiopathic pulmonary haemosiderosis which has become quiescent; it has, however, been followed by severe rheumatoid arthritis.

Case Report

The patient was born in January 1947, and at the age of 1 year she developed "pneumonia." Persistent pallor and cough followed, and she was admitted to Dudley Road Hospital, Birmingham, in March 1948. She was febrile and extremely pale; resonance was

impaired over the right chest. Investigations: haemoglobin 2.6 g./100 ml.; M.C.H.C. 29%; W.B.C. 9,200/c.mm.; reticulocytes 12.5%, 12%, 4%; R.B.C. fragility normal; bilirubin 0.4 mg./100 ml.; sternal marrow—intense normoblastic activity; chest *x*-ray film—indefinite inflammatory changes in right lung field. She appeared to make a satisfactory recovery after blood transfusion, and was discharged with a provisional diagnosis of Lederer's anaemia following a respiratory infection.

When seen 10 days later she appeared to be well, but slight haemoptysis had occurred, and chest *x*-ray examination showed mottling in the right lower zone. Over the next few months there were occasional haemoptyses; the haemoglobin varied from 9 to 11.9 g./100 ml. In September 1948 mottling in the right lower zone was more extensive radiologically. Further investigations showed: Mantoux 1/10,000 positive; gastric aspiration negative for alcohol- and acid-fast bacilli; E.S.R. 5 mm./hour.

She was readmitted in June 1949 with an exacerbation of symptoms. Chest *x*-ray examination showed increase of shadowing in the right lung, suggesting consolidation, and patchy consolidation in the left lung. Haemoglobin 10 g./100 ml.; reticulocytes 4%; serum bilirubin 1 mg./100 ml. Urine contained excess urobilinogen. A definitive diagnosis of idiopathic pulmonary haemosiderosis was made at this time.

Severe haemoptysis necessitated blood transfusion in December 1949. Finger-clubbing was noted and soon became marked. The right lung was now almost completely opaque on radiography. There were further admissions for acute exacerbations of cough and haemoptysis in 1950, 1951, 1953, and 1954 (twice). Haemoptysis ceased, however, in 1957, though she remained liable to episodes of respiratory infection with purulent sputum. Chest *x*-ray films showed progressive clearing: by 1958 the only abnormality was some accentuation of bronchovascular markings in the right middle lobe. Finger-clubbing had disappeared by 1960.

In December 1960 she developed pain, stiffness, and swelling in her hands and feet; the clinical appearance suggested rheumatoid arthritis. Investigation showed: haemoglobin 11.8 g./100 ml.; E.S.R. 37 mm./hour. Rheumatoid arthritis latex test positive. *X*-ray pictures of hands and feet were normal. There was progressive involvement of wrists, elbows, shoulders, ankles, cervical spine, and knees, with severe crippling, in spite of treatment with salicylates, phenylbutazone, hydroxychloroquine, and small doses of corticosteroids (1962–3).

At the time of writing (1965) respiratory symptoms were mild; she had a small amount of mucoid sputum most days, and occasionally developed "acute bronchitis." *X*-ray films of hands and elbows showed an extensive destructive arthritis; knees showed osteoporosis and erosions. Chest *x*-ray picture was normal. Haemoglobin 12.0 g./100 ml.; E.S.R. 33 mm./hour; blood urea 16 mg./100 ml.; serum iron 31 µg./100 ml.; total iron-binding capacity 196 µg./100 ml. No lupus erythematosus cells. Rose-Waaler test 1:64. Complement-fixation tests for antibodies to heart, liver, lung, thyroid, and kidney were negative. Urine was free of protein and sugar.

Discussion

The clinical course of the respiratory illness in this patient was typical of idiopathic pulmonary haemosiderosis. When she first presented with anaemia and recticulocytosis a haemolytic anaemia was suspected; this is a diagnostic pitfall (Wyllie *et al.*, 1948), particularly when there is elevation of serum bilirubin and excess urobilinogen. Finger-clubbing was present at one stage and later disappeared completely; this also occurred in Case 7 of Wyllie *et al.* (1948). The subsequent development of rheumatoid arthritis is of considerable interest, since its association with idiopathic pulmonary haemosiderosis has been observed on two previous occasions (Karlish, 1962; Dito and Ognibene, 1964; Ognibene and Dito, 1965).

It might be argued that such an association is merely the coincidental occurrence of a common and a rare disorder, since the incidence of rheumatoid arthritis is some 6% in the general population. The present patient, however, developed arthritis at the age of 14; at this age rheumatoid arthritis is rare, and the occurrence of two rare disorders suggests that they are causally related. Moreover, idiopathic pulmonary haemosiderosis and rheumatoid arthritis developed contemporaneously in the other two patients reported in the literature.

Other disorders which could be due to a disturbance of the immune mechanism have been recorded in association with idiopathic pulmonary haemosiderosis—for example, myocarditis (Campbell and Macafee, 1959; Murphy, 1965); glomerulonephritis (Heptinstall and Salmon, 1959); polyarthritis and glomerulonephritis (Leschke, 1957). Goodpasture's syndrome—pulmonary haemorrhage (purpura, haemosiderosis) and glomerulonephritis—is thought by many to be a variation of idiopathic pulmonary haemosiderosis (Elder *et al.*, 1965).

Search for circulating antibodies to human lung tissue has been unrewarding in idiopathic pulmonary haemosiderosis (Soergel and Sommers, 1962; Dito and Ognibene, 1964) and Goodpasture's syndrome (Scheer and Grossman, 1964). The latter authors did, however, demonstrate gamma-globulin attached to the glomerular basement membrane, which suggests, but does not prove, an immune process at this site; gamma-globulin was not demonstrated in lung tissue. In animals intravenous injection of heterologous antibodies to lung causes nephritis but no lung lesions.

The association of idiopathic pulmonary haemosiderosis with immune disorders does not necessarily indicate that idiopathic pulmonary haemosiderosis itself is due to an immune disturbance. Damage to pulmonary alveolar tissue by a variety of agents might initiate in some individuals an autoimmune process which damages the kidneys (as Sheer and Grossman suggest in Goodpasture's syndrome) or other non-pulmonary tissues. Whether rheumatoid arthritis could be caused in this way is not known, but Dito and Ognibene (1964) found that injection of idiopathic pulmonary haemosiderosis lung into a rabbit resulted in the development of a latex-fixing antibody and a rise in C-reactive protein. In another disorder with chronic pulmonary damage, diffuse fibrosing alveolitis, rheumatoid factor is commonly present (Turner-Warwick and Doniach, 1965; Mackay and Ritchie, 1965); moreover, pulmonary symptoms may precede the development of rheumatoid arthritis (Lee and Brain, 1962).

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