SHORT REPORTS

Respiratory Function in Rheumatoid Arthritis

In 1948 Ellman and Ball drew attention to the pulmonary manifestations of rheumatoid arthritis.¹ Nevertheless, until recently little attention has been paid to the possibility of pulmonary dysfunction in an appreciable proportion of patients, despite a normal chest x-ray result.^{2,3} The reported incidence of pulmonary involvement in rheumatoid arthritis shows considerable variation, ranging from 1.6% using radiological methods of detection alone,⁴ to 47% using respiratory function tests in addition to radiology.²

This investigation set out to study respiratory function with particular attention to diffusing capacity for carbon monoxide (DCCo) in patients with rheumatoid arthritis and a normal chest x-ray film.

Patients, Methods, and Results

A total of 85 patients (59 female, 26 male) fulfilling the American Rheumatism Association criteria for "classical" or "definite" rheumatoid arthritis were investigated. Those with abnormal chest x-ray films, anaemia, heart disease, or exposure to potentially harmful dusts were excluded. The duration of the rheumatoid disease was established, a detailed history taken, and a full clinical examination made. Radiological erosions were recorded and note made of past and present medication. Each patient had a chest x-ray examination, full blood count, E.S.R., antibody screen and the following respiratory function tests: spirometry; lung volumes; and gas transfer (DCCo). Sixteen of the patients had significant airways obstruction and were included in the study but grouped separately to allow for comparison. The results were compared with the predicted values and matched healthy controls.

The mean difference in the observed and predicted DCCo (Δ DCCo) in the male and female control subjects was not significant and was not significantly different from zero. There was a significant difference in Δ DCCo for the rheumatoid arthritis group, $P < 0.001$ the difference between the male and female groups also being significant ($P < 0.02$) (see table). The inclusion of those patients with airways obstruction was justified because the diffusing capacity in the groups with and without airways obstruction was not significantly different. Lung volumes were not significantly affected.

Observed minus Predicted DCCo (Δ DCCo) for Patients with and without Airways Obstruction, Controls, and Patients with R.A.

Group	Mean Δ DCCo	Standard Deviation (S.D.)	Standard Error of the Mean (S.E.M.)
Control (29)	0.98	3.13	0.58
R.A. male (26)	-5.51	5.83	1.14
R.A. female (59)	-2.48	3.95	0.51
No airways obstruction (71) ..	-3.34	4.96	0.59
Airways obstruction (16) ..	-3.71	3.96	1.02

A decreased DCCo correlated significantly only with smoking (correlation coefficient—0.48 $P < 0.02$) and the Rose Waaler and latex scores ($\log_2$ titre in women (—0.48, $P < 0.001$ and —0.42, $P < 0.001$)). The diffusing capacity was reduced by more than 20% in 44.7% of cases and exceeded 2 standard deviations below predicted in 18.4%. In the male patients the mean Rose Waaler and latex scores were higher but failed to show significant correlation with Δ DCCo. There was no correlation with the titre of antinuclear factor, nor was any particular antibody distribution associated with an impaired diffusing capacity.

Discussion

Significantly lower values of DCCo were found in the patients with rheumatoid arthritis, compared with the predicted values and the control group. As other factors had been carefully excluded, probably this observation represents a pulmonary manifestation of rheumatoid arthritis. Though we did not obtain material for histological examination, Frank *et al.* found changes compatible with early fibrosing alveolitis in all seven of their cases subjected to biopsy, of which at least two had a normal chest x-ray film.² It is, therefore, tempting to speculate that similar changes may be present in our patients. The equivocal antibody findings were not surprising, as if damage were immunologically mediated it may be by an immune-complex or cell-mediated mechanism not necessarily depending on the factors measured.

We were unable to confirm the suggestion by others⁵ of a relation between pulmonary manifestations in rheumatoid arthritis and treat-

ment with gold or steroids, and we found no relation with penicillamine medication.

We thank Dr. F. Dudley Hart for allowing us to study his patients, Dr. P. Emmerson for providing the facilities of the lung function laboratory, and Mr. David Brown for the statistical analysis.

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⁴ Walker, W. C., and Wright, V., *Annals of the Rheumatic Diseases*, 1969, 28, 252.

⁵ Talbott, J. A., and Calkins, E., *Journal of the American Medical Association*, 1965, 189, 911.

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Spongioform Myelinopathy in Premature Infants

Hexachlorophane (HCP) has recently been the subject of a restriction order under the 1968 Medicines Act, prompted by observations on the cutaneous absorption of HCP in newborn infants and by animal experiments showing that HCP may induce spongioform myelinopathy even after cutaneous application.¹ Nevertheless, because no deaths or toxic signs have been attributed to HCP under normal conditions of clinical practice, 3% preparations continue to be available under medical supervision.

We report here the isolation of considerable quantities of HCP from formalin-stored brain tissue from one of two premature infants with spongioform myelinopathy. Neuropathological findings have already been described.²

Patients and Methods

Both babies were girls and were born after 26 weeks gestation. The first weighed 980 g and needed intubation at birth but was well for the first 10 days, apart from jaundice, maximal on the third day 2.3 μ mol/l (bilirubin 14 mg/100 ml). Reflex activity and E.E.G. were normal. Apnoeic attacks began at 10 days, increased in frequency, and on the 24th day she became apnoeic and did not respond to treatment. A pneumothorax was found at necropsy.

Microscopic examination showed vacuolation in myelin of globus pallidus, brainstem, and spinal cord, but not in unmyelinated white or in grey matter. There was a generalized poverty of myelin compared with sections from other infants of the same gestation but of shorter survival time (half to four days) without vacuolation. The topographic distribution of myelinization was probably normal for age.

The second baby weighed 900 g. She was given resuscitation at birth and was satisfactory until apnoeic attacks started on the second day. These increased in severity, requiring periods of ventilation. At 72 hours serum bilirubin was 205 μ mol/l (12 mg/100 ml). Reflex activity on first and third days was normal. Fatal pulmonary haemorrhage occurred on the sixth day. Necropsy showed a small cerebral intraventricular haemorrhage. Microscopic changes in the brain and spinal cord were similar to the first case except that myelin poverty was less marked.

In both cases HCP in 3% detergent solution was applied daily with a swab to the face, napkin area, and umbilicus.

Formalin-stored samples of cerebral tissue and spinal cord were extracted by a method similar to that of Browning *et al.*³ Using an electron capture detector only 0.147 nmol/g (0.06 μ g/g) of HCP was found in cerebral tissue from case 1 but 1.60 nmol/g (0.65 μ g/g) from case 2. Similar amounts were found in the spinal cord. No HCP was present in the formalin used to store the tissue. The low level in case 1 was confirmed with the flame ionization detector, but in case 2 impurities with a similar retention time obscured the results.

Discussion

Even the lowest estimate of the HCP content of brain from case 2 is in the range found in experiments with monkeys in which spongioform myelinopathy was induced by 5 mg/kg injected daily for over a month

—brain levels of HCP varied between 0.442 and 1.204 nmol/g (0.18 and 0.49 µg/g).⁴ So myelinopathy in case 2 was probably attributable to HCP, despite the absence of clinical signs of toxicity. The trace level in case 1 suggests that myelinopathy was unrelated to HCP, for other causes of infantile spongiiform myelinopathy are known, though none has been identified in small premature infants. Nevertheless, case 1 may have lived long enough (24 days) for HCP to have been cleared from the brain. In rats HCP myelinopathy takes months to resolve, whereas the half-life of a dose of HCP is 19 hours.

Until now, the only direct evidence that HCP may cause myelinopathy in premature babies has been the correlation between spongy change and the extent of exposure to HCP.⁵ The amount of the compound recovered from our second case indicates that myelinopathy may result from the normal clinical use of a 3% solution of HCP on very immature infants.

¹ Lockhart, J. D., *Journal of Clinical Pharmacology*, 1973, 13, 445.

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⁴ Kimbrough, R. D., *Pediatrics*, 1973, 51, 391.

⁵ Powell, H., et al., *Journal of Pediatrics*, 1973, 82, 976.

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Slow Release Potassium Chloride Treatment

Preventing potassium depletion due to diuretic treatment is important. Kassirer *et al.* emphasized that potassium supplements should be as the chloride, as other salts tend to intensify any alkalosis caused by chloride loss and so perpetuate the loss of potassium.¹ After the recognition that potassium chloride tablets may cause ulceration and stenosis of the small intestine² Ciba claimed to have virtually overcome this problem by the introduction of Slow-K. Unfortunately, this has not removed the risk of life-threatening or even fatal adverse effects such as hyperkalaemia,³ oesophageal ulceration, and stricture. Here we draw attention to the last complication and suggest that Slow-K is sometimes contraindicated.

Case Report

A 42-year-old housewife with a history of rheumatic fever was first seen at the outpatient clinic in 1963 when aged 33. She had atrial fibrillation and signs of mitral and aortic incompetence. Cardiac screening showed enlargement of the left atrium. Digoxin treatment was begun and she was not seen again until 1971, when she was admitted to hospital in congestive cardiac failure. After being given frusemide and Slow-K 1.2 g, thrice daily, her failure resolved and cardiac catheterization was carried out in January 1972. The findings were consistent with aortic incompetence, mitral stenosis and incompetence, pulmonary hypertension, and tricuspid incompetence. In July she underwent tricuspid valve annuloplasty and mitral valve replacement with an aortic homograft. The postoperative course was satisfactory and she was discharged from hospital in August. She had continued treatment with digoxin, a diuretic, and Slow-K.

A few days after returning home she had difficulty in swallowing and this steadily led to considerable dysphagia. Discontinuation of digoxin did not bring relief and regurgitation of fluid and vomiting necessitated her re-admission to hospital. Barium swallow examination showed almost complete hold-up of barium just below the carina. The oesophagus was slightly dilated above this with a rounded lower margin changing to a very narrow track. Oesophagoscopy in late September 1972 confirmed the stricture in the mid-oesophagus and biopsy showed no evidence of malignancy. Successful bouginage was performed one week later, when a further biopsy again excluded malignant change. The patient was taught to pass bougies and subsequently she was able to eat solid food again.

Slow-K tablet lodged in mid-oesophageal region demonstrated by barium swallow.

Discussion

Dysphagia occurs only rarely in mitral valve disease despite the presence of even considerable enlargement of the left atrium. Chesshyre and Braimbridge⁴ described a patient with this complication after mitral Starr valve replacement, showing that the operation had resulted in a movement of the oesophagus to the left of its normal position. They concluded that this, in association with left atrial enlargement, caused sufficient compression of the oesophagus to hold up Slow-K and food producing irritation and stenosis. Pemberton reported oesophageal obstruction developing 10 days after mitral valve replacement, and oesophagoscopy showed mucosal ulceration of the posterior wall of the lower third of the oesophagus.⁵ This area was filled with white powder considered to be potassium chloride as the patient was taking Slow-K. We know of a similar case in a patient who complained of persistent pain on swallowing two weeks after operation for complete correction of Fallot's tetralogy. Barium swallow showed a Slow-K tablet lodged in the mid-oesophageal region (see figure).

The reports and the two cases, with quite different cardiac lesions indicate that Slow-K may be held up in the oesophagus with resultant dysphagia or even ulceration and stricture formation. Hence there is sufficient evidence to contraindicate the use of slow-release potassium chloride after cardiac surgery. It may also be advisable to avoid this preparation when cardiac or other disease, requires treatment involving a period of recumbency.

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² Baker, D. R., et al., *Journal of the American Medical Association*, 1964, 190, 586.

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⁴ Chesshyre, H. M., and Braimbridge, M. V., *British Heart Journal*, 1971, 33, 798.

⁵ Pemberton, J., *British Heart Journal*, 1970, 32, 267.

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