ALPHA$_1$-ANTITRYPSIN DEFICIENCY*

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The association between homozygous alpha$_1$-antitrypsin deficiency and chronic obstructive pulmonary disease was first described by Laurell and Eriksson in 1963[1] and since then numerous reports have confirmed and extended their observations. The concept envisages a relatively uninhibited proteolytic enzymatic process which is able to produce type A (emphysematous), type B (chronic bronchitic) or a mixed form of lung disease, depending on the site of maximum effect.[2] The first 2 South African cases with homozygous alpha$_1$-antitrypsin deficiency associated with severe obstructive airways disease are described in this paper together with studies of some members of their respective families.

The procedure used for measuring alpha$_1$-antitrypsin deficiency was that of Eriksson.[3] The normal range for this laboratory is 1·0 - 1·7 mg trypsin inhibited per ml of serum. Levels between 0·3 mg and 1·0 mg were regarded as denoting heterozygosity while a figure less than 0·3 mg conferred homozygous status.

CASE REPORTS

Case 1

The patient's first symptoms occurred in 1956, at the age of 27, when he noticed the presence of exertional dyspnoea. There was no cough or sputum production at this stage. During the next 6 years the dyspnoea worsened and, in addition, physical signs of hyperinflation and airway obstruction occurred. There was decreased cardiac and liver dullness, poor diaphragmatic movement, decreased breath sounds and expiratory rhonchi. In 1962 he first developed a cough which became productive only in 1966, by which time he was able to walk no more than 50 yards. At this stage he had the physical features of the type A (emphysematous or 'pink puffer') form of obstructive disease with severe obstruction, hyperinflation and hyperventilation at rest. In addition, there was also clinical pulmonary hypertension. Thereafter, he developed progressive respiratory failure with cor pulmonale and died in 1969. In the last year of his life he exhibited marked paranoia.

His cigarette consumption was 20/day for 20 years. As a child he had suffered from pneumonia, measles, whooping cough and mumps. There was a strong family history on his maternal side of lung disease, including pneumonia, asthma, chronic bronchitis and emphysema. Unfortunately none of these patients or their clinical records were available to us.

Initial chest X-rays in 1960 were normal. By 1967, however, there was marked flattening of the diaphragms with very little excursion, hypertranslucent lung fields, marked prominence of the pulmonary artery segment with attenuation of the peripheral vessels but no heart-chamber enlargement (Fig. 1). Later, during the last 18 months of his life, some right-sided enlargement of the heart developed. Electrocardiographic examination in 1960 (Fig. 2) showed a mean QRS frontal plane axis of about

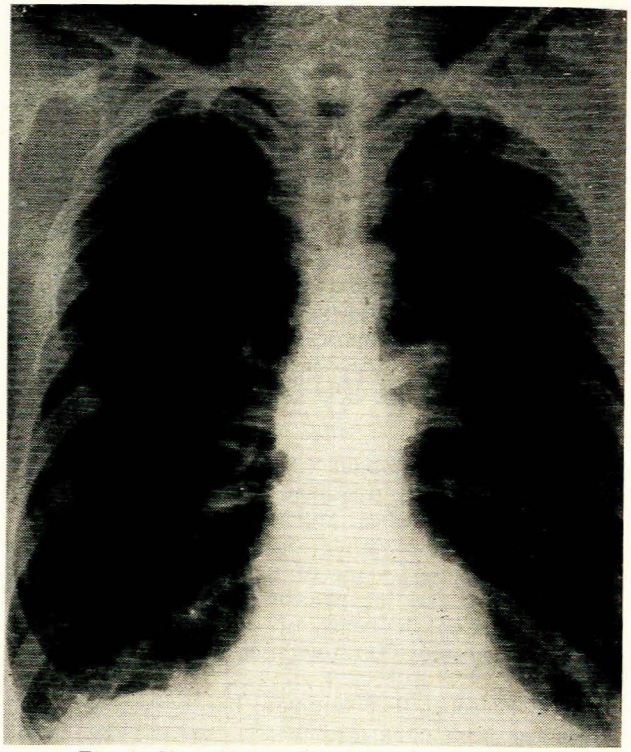

Fig. 1. Chest X-ray of case 1 taken in 1967.

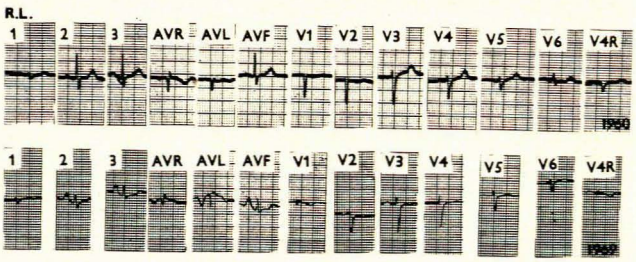

Fig. 2. Electrocardiograms of case 1 taken in 1960 and 1969.

90° and clockwise rotation. By 1969, there was very marked right atrial and right ventricular enlargement.

Full blood count, urea and electrolyte investigations were normal. His protein electrophoretic pattern showed the following results: albumin 4·33 g/100 ml, alpha$_1$-globulin 0·01 g/100 ml, alpha$_2$-globulin 0·53 g/100 ml, beta-globulin 0·99 g/100 ml and gamma-globulin 0·84 g/100 ml. Investigation of the tryptic inhibitory capacity of the serum showed 0·28 mg trypsin inhibited per ml of serum, and therefore a homozygous state.

Lung function studies were performed on 5 occasions

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between 1960 and 1969 (Table I). Vital capacity diminished on successive testing while there was increasing hyperinflation as represented by the rise in residual volume. There was progressive airway obstruction and arterial oxygen desaturation, the latter becoming more marked on exercise. Despite the hypoxaemia, the low arterial carbon dioxide tension demonstrates the alveolar hyperventilation characteristic of the 'pink puffer'. He eventually developed respiratory acidosis and died.

Specific studies of the tryptic inhibitory capacity of the patient's 3 daughters showed that all were heterozygotes. The figures measured in mg trypsin inhibited per ml serum were J.L. 0·98; L.L. 0·81; and T.L. 0·89. There was no clinical evidence of pulmonary disease in any of them. The patient's wife had normal antitryptic activity.

Case 2

The patient first developed a cough productive of white sputum in 1934 at 11 years of age. This cough persisted with sputum production being at first intermittent and later persistent, with occasional episodes of superimposed infection. By the age of 30 he had noticed the onset of exertional dyspnoea which was gradually progressive. He smoked heavily from the age of 16 for 20 years. A brother and a sister both had asthma. He was first seen at Johannesburg Hospital in 1962 suffering from pneumonia. On examination he was obese, slightly cyanosed, plethoric and showed evidence of cor pulmonale and right heart failure. In the chest diffuse rhonchi, poor breath sounds and hyperinflation were present. The haemoglobin was 18·7 g/100 ml with a packed cell volume of 60%. Chest X-rays showed hypertranslucent lung fields and flat, poorly moving diaphragms. The pulmonary artery segment and central pulmonary vessels were prominent but the heart was not enlarged. An electrocardiogram showed right atrial and right ventricular hypertrophy. Therapy with antibiotics, anti-failure drugs and bronchodilators was instituted and maintained, but the obstructive airways disease and cor pulmonale gradually progressed and he died in 1970. The clinical impression remained predominantly that of the type B or 'blue bloater' form of obstructive airways disease.

A marked feature on his final admission was the presence of diffuse bruising. Full coagulation and fibrinolytic studies were performed but no abnormality was detected. Serum protein electrophoresis was performed in 1969 and showed a total protein of 6·4 g/100 ml with an alpha$_1$-globulin of 0·10 g/100 ml. Serum antitryptic activity was measured and showed 0·347 mg trypsin inhibited/ml serum.

The patient's 5 children, who are well, and his wife also had their serum antitryptic activity measured. The figures measured in mg trypsin per ml serum were: Mr D. B., age 23 years, 0·76; Miss S. B., age 19 years, 0·72 Mr F. B., age 15 years, 0·64; Miss M. B., age 13 years, 0·88; and Miss L. B., age 10 years, 0·62. The patient's wife had normal antitryptic activity of 1·24 mg but the children are all heterozygotes. Despite the fact that the patient's measured level was slightly above the accepted figure for our laboratory it is highly probable that he was a homozygote.

Lung function tests performed in 1965 showed very severe obstructive airways disease with carbon dioxide retention, the latter feature being commonly present in the type B form of disease. Further tests performed in 1969 showed further carbon dioxide retention together with a greatly increased residual volume and marked arterial oxygen desaturation at rest (Table I).

DISCUSSION

The 2 homozygous patients described above have several common features such as an early onset of symptoms, death in early middle-age, strong family histories of pulmonary disease and asymptomatic heterozygous children. Equally important is the marked divergence in clinical presentation inasmuch as case 1 presented predominantly with type A (emphysematous) disease while case 2 tended towards the clinical features of type B (bronchitic) involvement. If the theory of alpha$_1$-antitrypsin deficiency is to be accepted it should explain both the common and apparently divergent features of these 2 patients.

Normally about 90% of serum antitryptic activity circulates as an alpha$_1$-globulin and is called alpha$_1$-anti-

TABLE I. LUNG FUNCTION STUDIES

	Case 1					*Case 2*	
	1960	*1962*	*1966*	*1967*	*1969*	*1965*	*1969*
Vital capacity litres measured	6·30	6·20	4·83	3·20	1·32	2·18	3·09
% of predicted value	111	108	86	58	24	43	62
Functional residual capacity litres measured	6·43	6·43	6·66		7·11		6·47
% of predicted value	151	151	158		169		156
Residual volume litres measured	3·62	3·58	4·65		6·74		5·54
% of predicted value	170	165	206		291		242
Total lung capacity litres measured	9·92	9·78	9·48		8·06		8·63
% of predicted value	126	123	121		102		118
MVV_F litre/min measured	98	96	44	35	8	22	24
% of predicted value	57	55	27	21	6	16	18
FEV_1 litres	2·07	2·23	1·08	0·8	0·37	0·50	0·65
Rest ventilation litres/min	12·0	16·4	17·8	16·0	7·9		10·4
Arterial O_2 saturation %—rest	90	91	82	80	88·5*		71·5
Arterial O_2 saturation %—ex.	82	77	61	59			
Blood pH			7·395	7·43	7·315	7·38	7·43
Blood PCO_2 mmHg			30·5	29·0	49·0	48·5	89·0

*Patient was breathing O_2 continuously and tolerated only 2 minutes without it, when this measurement was made.
Techniques and predicted values used have been published previously.[4-7]

trypsin. In some patients with chronic obstructive pulmonary disease, a decrease in alpha$_1$-antitryptic activity has been found, the defect probably being carried via an autosomal-recessive gene. Thus homozygous patients having about 10% of normal activity, and heterozygotes, having about 50% of the normal value, have been described.[8]

Alpha$_1$-antitrypsin or very similar globulins inhibit several other proteolytic enzymes besides trypsin, such as chymotrypsin, plasmin, thrombin[9] and elastase,[10] as well as the digestive enzymes released from leucocytes.[11] The theory claims that deficiency of antitryptic activity permits digestion of protein. Thus continual slow release of poorly inhibited proteolytic enzymes from alveolar macrophages, leucocytes and other phagocytic cells may result in digestion of alveolar septa producing panacinar emphysema or type A disease. In those cases where there is chronic bronchial irritation by agents such as cigarette smoke, recurrent infections, or air pollution, the leucocytic enzymes would be concentrated in the airways and the lack of proteolytic inhibition could result in predominant chronic bronchitis and centrilobular emphysema (type B disease).[2] Obviously a combination of the 2 types of disease could occur.

It is possible that part of the bronchitic element in case 2 could be ascribed to the patient's cigarette smoking, but coughing had begun at the age of 11 years, 5 years before he had started smoking. In Eriksson's series[3] about half of his homozygous-deficient patients had evidence of chronic bronchitis and chronic cough before the onset of dyspnoea.

There appears to be a definite association between the homozygous state and obstructive airways disease, especially panacinar emphysema, the incidence varying from 1 to 10%[12,13] or more[14-16] depending on the group of patients studied. Whether heterozygotes have an increased liability to disease is still disputed. Some authors have not found this association,[17,18] while others[14] have claimed that heterozygous subjects do have an increased liability to pulmonary involvement. Lieberman,[14] in fact, found that 15·2% of 66 patients hospitalized with pulmonary emphysema had heterozygous alpha$_1$-antitrypsin deficiency. The over-all incidence of the deficiency was 25·8% in this group. Of patients under the age of 50 years, 47·8% had deficient levels. If such observations are confirmed, the role of alpha$_1$-antitrypsin activity will assume a position of great importance in this increasingly common disease. It must be emphasized, however, that not all people with the deficiency—even homozygotes—will develop disease, and other factors must therefore be operable as well.

The best and simplest screening test for alpha$_1$-antitrypsin deficiency is protein electrophoresis, preferably performed by the cellulose acetate method.[19] An alpha$_1$-globulin level of less than 0·20 g/100 ml should be followed by a more specific test for antitrypsin deficiency. The most commonly used method is the enzymatic measurement of the trypsin-inhibitory capacity of the serum as performed in our cases described above. Alternative techniques such as immunodiffusion[20] or antigen-antibody-crossed electrophoresis[21] have also been described. It should be noted that, especially in a heterozygote, infection,[22] pregnancy[15] or contraceptive pills[3] may raise the levels of alpha$_1$-antitrypsin into the normal range.

Since antitryptic activity also functions against other proteolytic enzymes, it was thought that increased fibrinolytic activity might be present, especially in the second patient, who bruised very easily. However, full testing failed to disclose any defect. Possibly, since there is a large degree of functional reserve in antifibrinolytic activity, an additional situation involving increased fibrinolysis might bring out such a tendency.

SUMMARY

The first 2 cases of homozygous alpha$_1$-antitrypsin deficiency in South Africa are described, together with evidence demonstrating the heterozygous status of their children. Their clinical courses and special investigations are described illustrating that these cases may present with either predominantly emphysematous or bronchitic features. The condition is reviewed and the methods and importance of diagnosis are pointed out.

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