Medicine in the Elderly

Three cases of alpha-1-antitrypsin deficiency in the elderly

C.I.A. Jack and C.C. Evans

Royal Liverpool Hospital, Prescot Road, Liverpool, UK

Summary: We report three elderly patients who presented with increasing dyspnoea on exertion and radiological evidence of basal bullous emphysema. On further investigation they were found to have alpha-1-antitrypsin deficiency.

We emphasize that alpha-1-antitrypsin deficiency can present much later than is usually the case especially if the patient is a life-long non-smoker.

Introduction

We report three cases of alpha-1-antitrypsin deficiency presenting for the first time in elderly patients (average 72 years) as chronic airflow limitation. All three patients were life-long non-smokers, and had no relevant family history or evidence of hepatic involvement.

Previous reports have emphasized early presentation with emphysema in young or middle-aged adults, cryptogenic cirrhosis in children and non-B chronic active hepatitis in young adults.^{1,2} There is also an association between rheumatoid arthritis and reduced α -1-antitrypsin levels^{3,4} and case reports linking uveitis, thyroiditis, vasculitis and glomerulonephritis with α -1-antitrypsin deficiency.^{5–7} We believe that alpha-1-antitrypsin deficiency should be sought in patients with clinical and radiological features of emphysema irrespective of age so that advice may be offered to other family members.

Case reports

Case one

A 69 year old female retired accounts officer presented with an 8-year history of increasing shortness of breath. On presentation she had an exercise tolerance of 50 metres on the flat. She also complained of an exertional wheeze but had minimal cough. She was one of six children and

none of her siblings had any history of lung disease. She was a life-long non-smoker.

On examination she was dyspnoeic, cyanosed and thin. Cardiovascular system revealed evidence of pulmonary hypertension with a right ventricular heave and palpable pulmonary second sound. She had a barrel shaped chest with widespread wheeze on forced expiration. Investigations, including full blood count and immunoglobulins, were normal; blood gases revealed type I respiratory failure with a PO_2 of 5.6 kPa. Her electrocardiograph showed P pulmonale and her chest radiograph basal bullous emphysema (Figure 1). Full pulmonary function studies, including a flow volume loop, were consistent with a diagnosis of emphysema. The serum alpha-1-antitrypsin level was determined at 0.22 g/l (normal range 1.3–3.4 g/l) with a proteinase inhibitor (Pi) phenotype piZZ.

Case two

A 65 year old retired chemist presented with a 10-year history of recurrent chest infections associated with a productive cough. He also complained of increasing shortness of breath on exertion associated with wheeze. His past medical history and family history were unremarkable. He was a life-long non-smoker. The only positive physical findings were coarse inspiratory crackles at the right base and widespread expiratory wheezes.

Investigations, including full blood count, immunoglobulins and electrocardiograph, were all normal; blood gases showed hypoxia PO_2 7.7 kPa (on air). His chest radiograph revealed basal bullous emphysema. Spirometry showed a marked increase in the residual volume with a reduction in

Correspondence: C. Jack, M.R.C.P., Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

Accepted: 22 April 1991

Figure 1 Chest X-ray showing basal bullous emphysema.

lung transfer factor in keeping with a diagnosis of emphysema. The flow volume loop showed the classical steep curve of emphysema. The serum alpha-1-antitrypsin level was determined at 0.37 g/l, well below the normal range (1.3–3.4 g/l), and the phenotype was PiSZ.

Case three

An 82-year old retired postman presented with a 3-year history of increasing shortness of breath on exertion. Exercise tolerance at presentation was 200 metres on the flat. He complained of a wheeze and was coughing about 20 ml of clear sputum daily. He had undergone an intestinal resection in the past for suspected lymphoma and apart from an episode of pneumonia in 1988 he had remained well on no medication. He came from a large family with no history of lung disease. On examination there was no lymphadenopathy. The respiratory system revealed inspiratory crackles at the right base with widespread wheeze on expiration.

Investigations, including full blood count, immunoglobulins and electrocardiograph, were normal. Blood gases revealed hypoxia, his chest X-ray showed basal bullous emphysema confirmed by full pulmonary function tests with a flow volume loop consistent with emphysema. The alpha-1-antitrypsin level was 0.4 g/l (normal range 1.3–3.4 g/l) with a phenotype PiZZ.

Discussion

Alpha-1-antitrypsin is a glycoprotein synthesized in the liver. It is an acute phase reactant² and is a major proteinase inhibitor participating in many inflammatory processes occurring within the body. The clinical syndrome of alpha-1-antitrypsin deficiency was first observed in 5 subjects by

Laurell and Eriksson during routine analysis of electrophoretic strips.⁸ It is composed of 294 amino acids,⁹ with a molecular weight of 52000 and has a half life of 4–5 days *in vivo*.

The alpha-1-antitrypsin gene is a single gene of 12.2 Kb, located as a pair of co-dominant autosomal alleles on chromosome 14 at q31–32.3^{10–12} and is composed of 7 exons and 6 introns.¹³ It appears to be highly susceptible to genetic mutations which result in the formation of many variants and are readily classified by isoelectric focusing methods. These variants are most likely the result of single amino acid substitutions⁹ and only a few are clinically significant. Over 90% of the population show the proteinase inhibitor PiMM phenotype. Other clinically significant phenotypes include PiSS, PiSZ, PiZZ and Pinull null. These different phenotypes give rise to varying plasma levels of alpha-1-antitrypsin; thus PiZZ gives 15% of normal levels.

Alpha-1-antitrypsin is a ubiquitous enzyme but its greatest clinical importance is the protective effect on alveolar walls. By its nature, lung tissue is exposed to environmental factors predisposing to infection and inflammation. Alpha-1-antitrypsin is preferentially incorporated and remains active for longer periods of time in lung tissue compared to other body sites. The alveolar structure of the lungs is composed of elastin and other macro-molecules. These may be destroyed by neutrophil elastase resulting in emphysema. Alpha-1-antitrypsin prevents the function of neutrophil elastase by binding to it to produce an inactive complex¹⁴ and hence limiting parenchymal damage. Alveolar wall destruction occurs mainly at the bases in alpha-1-antitrypsin deficiency.¹⁵ This is attributed to the higher blood flow in these basal segments and hence a greater concentration of polymorphs with the ability to release neutrophil elastase.¹⁶

In contrast, cigarette smokers develop apical emphysema. The currently accepted explanation for this distribution of alveolar wall destruction is the activation of pulmonary macrophages by irritants.¹⁶ Due to the ventilation/perfusion ratio in the lungs a greater number of macrophages are stimulated in the upper lobes and once activated they release neutrophil elastase, resulting in alveolar destruction. In alpha-1-antitrypsin-deficient patients who are also cigarette smokers, the distribution of tissue damage is mainly basal. Cigarette smoking is the major contributing factor in both normal and alpha-1-antitrypsin deficient individuals.^{16,17} It is interesting to note that all our patients presented later in life and all were life-long non-smokers. This correlates with other previous studies. In a New Zealand study¹⁸ the average age for the onset of dyspnoea was 32 years in 14 cigarette smokers compared to 51 years in 8 non-smokers. In this study only 48% (33 out of 69

patients) had clinical evidence of emphysema. In our small series the average age at presentation was 72 years and all of our patients had symptoms, signs, radiological and spirometric evidence of emphysema.

In conclusion, we believe that alpha-1-antitrypsin deficiency should be considered in any patient, regardless of their age, who presents with increas-

ing dyspnoea and has radiological evidence of basal emphysema. In families of our patients no children or siblings were affected, but if a heterozygous spouse had been identified it would have been essential to phenotype the offspring and offer counselling and appropriate anti-smoking advice.

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