Thorax 1989;**44**:758–759

Heterozygous FZ α_1 antitrypsin deficiency associated with severe emphysema and hepatic disease: case report and family study

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ABSTRACT A patient with advanced emphysema and cor pulmonale had the changes of α_1 antitrypsin deficiency in a liver biopsy specimen and was shown to have the phenotype PiFZ. This case supports the contention that the *F* allele of α_1 antitrypsin predisposes to the development of emphysema, particularly when it occurs in conjunction with the *Z* allele.

The association between PiZZ α_1 antitrypsin deficiency and the development of emphysema and cirrhosis is well recognised.[1,2] It is less clear whether other, more unusual α_1 antitrypsin phenotypes are associated with pulmonary or hepatic disease.[3] The uncommon F variant of α_1 antitrypsin was first described by Fagerhol *et al.*[4] The FZ phenotype is rare, occurring in about 1/17 000 of the population, but may be associated with an increased risk for the development of obstructive lung disease.[5]

Case report

A 56 year old woman presented with drowsiness and oedema. She had a chronic non-productive cough and had had occasional respiratory tract infections. She had smoked on average five cigarettes a day for 40 years; her alcohol intake was minimal. On examination she had central cyanosis; her jugular venous pressure was substantially raised; and there was gross peripheral oedema, ascites, and tricuspid incompetence with pulsatile hepatomegaly. Investigations indicated a mixed metabolic and respiratory acidosis, polycythaemia, and mildly abnormal liver function (pH 7·26, arterial oxygen tension (Pa_{O_2}) 5·7 kPa, arterial carbon dioxide tension (Pa_{CO_2}) 6·5 kPa, bicarbonate 15·7 mmol/l, haemoglobin 17·3 g/dl, alkaline phosphatase 261 (normal 30–100) IU/l), prothrombin ratio 1·2, lactate dehydrogenase 168 (normal 100–350) IU/l, aspartate aminotransferase 38 (normal 7–40) IU/l)).

The patient responded to treatment with resolution of the ascites, peripheral oedema, and tricuspid incompetence, though arterial blood gases remained abnormal (pH 7·42, Pa_{O_2} 5·3 kPa, Pa_{CO_2} 5·9 kPa, bicarbonate 27 mmol/l).

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Accepted 26 May 1989

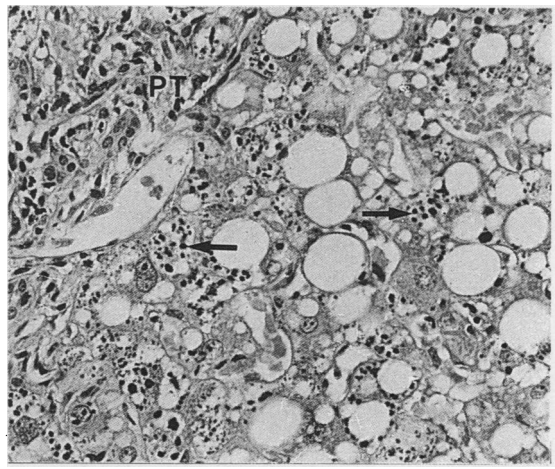

Fig 1 *Portal tract (PT) with periportal liver cells showing fatty change and numerous globules (arrows), staining with periodic acid Schiff, of varying sizes. (Diastase PAS.)*

Pulmonary function tests showed substantial and irreversible airways obstruction with air trapping (FEV_1 0·8 (expected 2·3) l, vital capacity 2·1 (expected 3·1) l, FEV_1/VC 38%, residual volume 2·2 (expected 1·7) l, residual volume/total lung capacity 51% (expected 35%)). The serum α_1 antitrypsin concentration was 2·23 (normal 1·9–3·5) g/l.

A liver biopsy, performed because of her hepatomegaly, showed numerous diastase resistant, periodic acid-Schiff positive globules in hepatocytes of zones 1 and 2, which immunoperoxidase staining showed to be positive for α_1 antitrypsin (fig 1). There was slight expansion of portal tracts by fibrosis with some bile duct reduplication. Moderate fatty change, sinusoidal congestion, and dilatation were also evident. Serum electrophoresis showed the patient's α_1 antitrypsin phenotype to be PiFZ. After discharge from hospital she stopped smoking and remains stable. The serum α_1 antitrypsin concentration (1·56–1·67 g/l in repeated tests) is now below the normal range.

Family study

All consenting first degree relatives of the proband were seen and had a history taken, an examination, α_1 antitrypsin phenotyping (isoelectric focusing on polyacrylamide gel), measurement of serum α_1 antitrypsin concentration (single

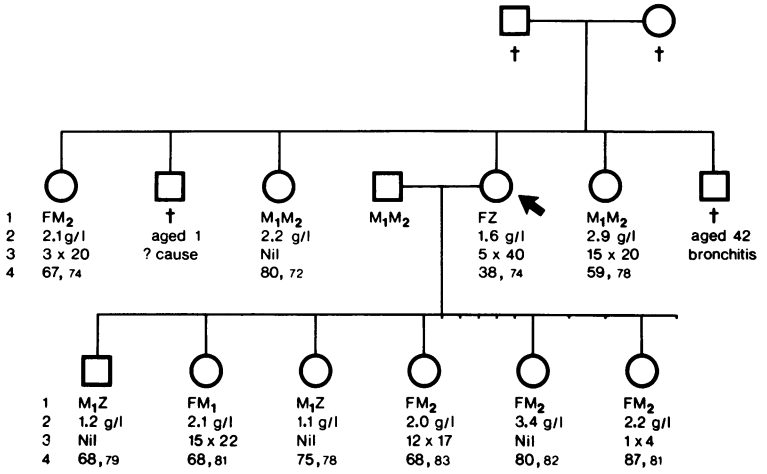

Fig 2 *Family pedigree of proband showing Pi type, serum α_1 antitrypsin concentration, smoking history, and FEV_1/vital capacity (VC)% of the proband, her three surviving siblings and the six of her fourteen children who were available for study. 1—Pi phenotype; 2—serum α_1 antitrypsin concentration; 3—number of cigarettes a day × years; 4—FEV_1/VC% and % predicted; ↖ proband; †deceased.*

radial immunodiffusion, Behring), measurement of lung function and volumes (FEV_1 and vital capacity (Vitalograph), residual volume, and total lung capacity (helium dilution, P K Morgan)), and liver function tests.

None showed evidence of liver disease. Alpha$_1$ antitrypsin phenotype, serum α_1 antitrypsin concentrations, and lung function values are shown in figure 2. The phenotype of the proband (PiFZ) was confirmed by two other laboratories.

Discussion

This PiFZ patient presented with respiratory failure and cor pulmonale and had severe, fixed airways obstruction with air trapping. Liver biopsy showed abnormalities characteristic of α_1 antitrypsin deficiency. These changes have previously been reported in other heterozygous PiZ states—for example, PiMZ and PiSZ.[6] Although some portal fibrosis was detected this did not amount to cirrhosis and the results of liver function tests returned to normal after treatment of her cardiorespiratory disease. Her α_1 antitrypsin was in the low normal range at presentation when she was seriously ill and subsequently fell to below normal concentrations similar to those seen in four other PiFZ patients.[5-7] This illustrates the importance of α_1 antitrypsin phenotyping in identifying individuals with heterozygous α_1 antitrypsin deficiency, as α_1 antitrypsin is an acute phase reactant and concentrations may be temporarily raised during acute illness.

Four previous reports have suggested an association between the PiFZ phenotype and pulmonary disease. Two of these[8 9] give no details of clinical condition or pulmonary function. Cockcroft *et al*[7] described three PiFZ siblings with moderately severe airways obstruction and a mean serum α_1 antitrypsin concentration 58% of that seen in PiMM individuals. Beckman *et al*[5] report a PiFZ patient with "bronchitis" (FEV_1/FVC 82%), whose α_1 antitrypsin concentration was 53% of the normal mean. No reference was made to the patient's hepatic state in these reports. Brand *et al*,[10] however, reported a PiFZ non-smoking patient with cirrhosis but no evidence of emphysema.

None of the proband's three surviving siblings or of the six children available for study shares her FZ phenotype. The death of her brother at the age of 42 from "bronchitis" raises the possibility that he too had pulmonary disease associated with α_1 antitrypsin deficiency. Two of the proband's children are PiMZ and have substantially reduced concentrations of serum α_1 antitrypsin (fig 2). Both are non-smokers and show only a mild reduction in FEV_1/VC%. Four of the five relatives with the FM phenotype have a slightly low serum α_1 antitrypsin level at around 2·1 g/l (77% of the normal mean). Beckman *et al*[5] reported α_1 antitrypsin concentrations in 12 PiFM individuals as being 90% of the normal mean and suggested these individuals had an increased risk of airways obstruction that was independent of their serum α_1 antitrypsin concentration.

This report supports the contention that the *F* allele of the α_1 antitrypsin gene predisposes to the development of emphysema if it occurs with another deficiency allele, in particular Z. Our patient's obstructive airways disease was particularly severe by comparison with previously reported cases of PiFZ associated emphysema. We have shown that the histological changes of α_1 antitrypsin deficiency found by liver biopsy occur in association with the FZ phenotype.

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