Mild pulmonary, but severe hepatic disease in a cystic fibrosis patient homozygous for a frameshift mutation in the regulatory domain of the CFTR

The clinical phenotype of cystic fibrosis (CF) patients is very variable and it has been suggested that patients lacking the cystic fibrosis transmembrane conductance regulator (CFTR) have milder lung disease than those having an altered CFTR. However, on the basis of the large variation in lung function in patients homozygous for the most common CF mutation, AF508, and W128X homozygotes, it was concluded that most CF patients have a common phenotype, but that other genetic and environmental factors may affect outcome. We describe a patient, homozygous for a frameshift mutation in the regulatory domain (R) of the CFTR, who presented with mild lung disease but severe hepatic and pancreatic involvement. The mutation, 2184delA (deletion of A at position 2184 together with an A to G substitution at position 2183 in exon 13) was originally characterised by D Boton and L-C Tzou (personal communication) and was found in both parents of our patient in a screening programme of non-AF508 CF chromosomes with denaturing gradient gel electrophoresis, followed by sequencing. The boy was born at term in December 1977, birth weight 3500 g, to healthy, non-consanguineous parents. Cystic fibrosis presented neonatally with meconium ileus which was treated surgically. CF was confirmed by positive pilocarpine iontophoresis sweat test at 10 days. Conventional treatment for CF was given. The clinical course of the lung disease was mild. At the age of 5 years a nasal polypectomy was performed. Liver function tests altered from this age onwards. Hepatomegaly was observed two years later. He was admitted to hospital at the age of 11 years for intravenous antibiotic treatment because of pulmonary infection. Pseudomonas aeruginosa was isolated from sputum cultures soon after this, but not repeatedly. At 13 years he was asymptomatic with discrete clubbing, hepatomegaly of 4 cm, and puerperal state A1PIG2. Weight and height were between the 10th and 25th centiles. Respiratory function tests for FVC, FEV1, and PEFR were 89%, 83%, and 76% of predicted, respectively. Schuchman score was good (80/100) as was the Chisvin-Norman score at 9DAB. ALT (71 IU/l, normal <29 IU/l) and yGT (106 IU/l, normal <40 IU/l) values were raised. Ultrasonographic investigations showed marked liver and pancreatic steato-cirrhosis.

In conclusion, we present a patient homozygous for a frameshift mutation in the R domain of the CFTR. He has severe pancreatic and hepatic disease, but lung disease is mild. The 2184delA mutation predicts a stop codon 38 amino acids further in the same exon of the CFTR, but it is not known whether this mutation results in the total absence of the CFTR or in a partially functional protein. Study of the CFTR protein in different tissues will be necessary to resolve this. At the moment, the question remains whether these studies will clarify the difference in disease expression in tissues.

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