Pulmonary function in children with homozygous alpha₁-protease inhibitor deficiency

Abstract  Alpha₁-protease inhibitor (alpha₁-PI) deficiency is a well-recognized cause of emphysema in adults; however, the natural history of this disorder in children is unclear. Because of the paucity of data in the paediatric age group, we performed whole body plethysmography, spirometry, and diffusing capacity, in a cohort of 17 homozygous (PiZZ phenotype) children (9 females, 8 males; mean age ± SEM 13.4 ± 0.9, range 7–18 years) and in 17 normal schoolchildren (13.5 ± 0.9, 7–18 years), using a matched-pair design. Blood was drawn for determination of serum alpha₁-PI levels, PI phenotype, and standard biochemical tests of liver function. Among the PiZZ subjects, 12 were detected during diagnostic workup of prolonged neonatal icterus, and 5 by routine testing in paediatric patients. None had chronic respiratory symptoms except for an 18-year-old PiZZ girl with a history of recent onset of exertional dyspnoea. All were non-smokers. The Wilcoxon test was used for statistical analysis. As expected, serum alpha₁-PI levels were lower in the PiZZ group (16% of the control value). A few patients had slight elevations of their liver enzymes. As for the pulmonary function parameters, differences between groups were not significant. Individual data showed no consistent abnormality in lung function except for signs of mild expiratory obstructive airway disease with hyperinflation (elevated TGV/TLC ratio) in the only symptomatic 18-year-old subject (0.63, control subject 0.49). This was unresponsive to bronchodilators. For her, augmentation therapy with intravenous infusions of alpha₁-PI may be considered.

Conclusion Our study confirms the absence of pulmonary function abnormalities in the vast majority of children with homozygous alpha₁-PI deficiency. Serial measurements of lung function may help to distinguish those individuals who require treatment with alpha₁-PI from those who do not.

Key words  Alpha₁-protease inhibitor deficiency · PiZZ phenotype · Children · Pulmonary function

Abbreviations  Alpha₁-PI alpha₁-protease inhibitor · FEV₁ forced expiratory volume in 1 s · FRC functional residual capacity · FVC forced vital capacity · MEF maximal expiratory flow · PEF peak expiratory flow · TGV thoracic gas volume · TLC total lung capacity
Introduction

Alpha-protease inhibitor (alpha-PI), formerly called alphal-antitrypsin, is a serum protein that is capable of inhibiting several types of proteolytic enzymes. The discovery of an association between homozygous alpha-PI deficiency and emphysema in young adults 30 years ago led to the hypothesis that emphysema was caused by an imbalance between proteases and antiproteases in the lung [14]. However, the natural history of pulmonary involvement in children with this metabolic disorder is unclear. Children present typically with liver disease in early infancy [2]. Although there are isolated reports of panacinar emphysema in children [6, 8, 11, 19, 20], serial lung function tests in a group of adolescents were reported as normal [21]. In contrast, there was a tendency for hyperinflation in another group of young children with liver disease due to alpha-PI deficiency [10]. The evaluation of lung function in children with alpha-PI deficiency is important now that therapy with human plasma-derived alpha-PI has become available [1]. Moreover, individuals with this disorder should be strongly advised towards a non-smoking lifestyle, as epidemiological data clearly show that smoking accelerates the development of emphysema in these subjects [12]. Because of the paucity of data, we studied pulmonary function of a group of asymptomatic adolescents with homozygous alpha-PI deficiency (PiZZ variant) in order to better define early functional impairment before the appearance of symptoms.

Subjects and methods

Seventeen PiZZ children participated in the study. They were diagnosed as being alpha-PI deficient either during diagnostic workup of prolonged neonatal icterus (n = 12) or by routine testing in children admitted to the children’s hospital at the University of Lübeck/Germany (n = 5). Alpha-PI typing by isoelectric focussing was done in the case of low alpha-PI levels. The controls were normal schoolchildren. All children were nonsmokers. They were considered healthy by their parents, and none had evidence of respiratory infection in the 4 weeks before the study. Written informed consent was obtained from each subject and, in the case of minors, from their parents. The investigation was approved by the Medical University Lübeck ethics committee.

A physical workup was done in the patients and the controls, and blood was drawn for standard biochemical tests of liver function including bilirubin, aspartate and alanine aminotransferase, and gamma-glutamyl transeptidase. Serum alpha-PI levels were measured using rate nephelometry [18], and alpha-PI typing was done by isoelectric focussing on polyacrylamide gel [7].

Airway resistance was determined during quiet breathing, and thoracic gas volume was measured at functional residual capacity with a constant-volume body plethysmograph (Masterlab; E. Jaeger, Würzburg, Germany). Baseline sph'ometry was performed with a pneumotachograph whose differential pressure signal was electronically integrated to give volume. Parameters measured were forced vital capacity (FVC), forced expiratory volume in the 1st s (FEV1), FEV1/FVC, peak expiratory flow (PEF), and maximal flows at 75%, 50% and 25% of vital capacity (MEF75, MEF50, MEF25). Functional residual capacity (FRC) was measured by the helium dilution method using a water-sealed bell spirometer (Pulmonet 3, Gould/Godart, Einthoven, Holland). Single-breath carbon monoxide diffusing capacity was then performed (Fenyves and Gut, Basel, Switzerland).

Each alpha-PI deficient child was closely matched with a child from the control group with regard to sex, age, height and weight.