Unusual Abnormalities in Adolescent Siblings with $\alpha_1$-Antitrypsin Deficiency*

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We studied, over a four-year period, two adolescents with $\alpha_1$-antitrypsin (AAT) deficiency who subsequently died from complications of hepatic cirrhosis. Serial pulmonary function studies indicated mild obstructive lung disease involving peripheral airways in both patients. Postmortem histologic and pulmonary morphometric studies indicated mild diffuse airspace and bronchial gland enlargement, and slight dilation of small airways. This airspace enlargement may represent the early stage of lung disease in AAT-deficient subjects and suggests that pulmonary anatomic changes may occur long before the onset of clinically and pathologically significant emphysema.

$\alpha_1$-antitrypsin (AAT) deficiency was first described by Laurell and Eriksson in 1963.1 They later described the relationship of this deficiency with obstructive emphysema in adults.2 Juvenile pulmonary disease is not a common presentation of AAT deficiency, although a 15-year-old boy with emphysema was included in an early report by Eriksson.3 Several theories of pathogenesis have been proposed relating AAT deficiency and panacinar emphysema.4 Most theories assume tissue is destroyed by enzymes normally inhibited by AAT. However, the time course for developing such pulmonary lesions is poorly understood due to a lack of morphometric studies on AAT-deficient children’s lungs. We obtained serial pulmonary function tests (PFTs) on two AAT-deficient adolescents who died primarily from complications of liver disease. We also report morphometric measurements of the lung in one of these children. The observations in these two patients suggest that airspace enlargement may begin at an early age in AAT-deficient individuals.

**Case Reports**

**Case 1**

This girl was one of nine siblings born to healthy parents. She had a normal infancy except for prolonged jaundice during the first few weeks of life. At age four years, hepatosplenomegaly was noted, and a liver biopsy specimen study disclosed idiopathic portal cirrhosis. Progressive hepatic enlargement developed, and at age nine years digital and scleral angiomas were noted. At age 13 years four months, she received a diagnosis of AAT-deficiency, phenotype ZZ. Chest roentgenograms (Fig 1) showed slight hyperinflation with diffusely increased interstitial markings. For two years prior to her death, she complained of poor visual acuity, frequent headaches, and multiple joint pains. She had severe digital clubbing and typical changes of pulmonary osteoarthropathy. She occasionally had episodes of acute bronchitis, with increased sputum production, which resolved with tetracycline therapy. Persistent cyanosis and pretaill edema developed when she was 15. While breathing room air she had a PaO$_2$ of 59 mm Hg, PaCO$_2$ of 23 mm Hg, and pH of 7.40. She had a hematocrit reading of 48 percent, a normal prothrombin time while taking vitamin K, and a chronically elevated bilirubin level of approximately 3 mg/dl. At age 16 years five months, while riding in an airplane, she experienced an acute left-sided headache and right body paresis. She died several days later from intra cranial and intrapulmonary hemorrhages. She had never smoked any form of tobacco.

**Case 2**

This patient was the youngest brother of case 1. When case 1 received the diagnosis of AAT-deficiency, case 2 also underwent studies and had a AAT level of 53 mg/dl and phenotype ZZ. Case 2 had a normal infancy, but by age two developed splenomegaly. At age seven, he had a splenectomy, and a liver biopsy study demonstrated cirrhosis. At age 13, he experienced an upper gastrointestinal hemorrhage from esophageal varices. He also had severe clubbing and was cyanotic with exercise. At age 15½ years, he began noting digital angiomas, and a pulmonary radionucleotide shunt study disclosed a 50 to 55 percent right-to-left pulmonary shunt. His hematocrit reading was 50 percent, bilirubin level was 1 to 2 mg/dl, and his prothrombin time was prolonged. He never experienced significant pulmonary symptoms, although radiologically he had mild hyperinflation (Fig 2). When he was aged 16 years three months, a severe headache with fever developed, followed by his second major upper gastrointestinal hemorrhage. The next three days were complicated by an esophageal perforation, left pneumothorax, and progressively worsening neurologic signs. He died several days later from a ruptured cerebellar abscess. He had never smoked any form of tobacco.

**Methods**

Pulmonary function tests (PFTs) were obtained on both patients, and results are reported as percent of predicted normals,5 unless otherwise noted. Forced vital capacity (FVC), forced expiratory volume in one second (FEV$_1$), and maximum mid-expiratory flow rate (FEF25-75%) in room air were calculated from volume-time spirometric studies. Maximum flows at 50 percent and 75 percent of exhaled vital capacity (FEF 50% and FEF 75%) were measured from maximum expiratory flow volume curves as de-

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Adolescent Siblings with Alpha, Antitrypsin Deficiency (Wagener et al)
FIGURE 1. Chest roentgenograms of case 1 obtained one year before death. Films are typical of changes prior to sudden deterioration. Extensive increase in lung markings is the predominant pulmonary feature; hyperinflation is also present.

Lung volumes were measured in a 600-L, variable volume, pressure-compensated body plethysmograph using the technique of Dubois and colleagues. Pulmonary morphometric measurements were done on case 2's lungs, using methods previously described from our laboratory. Briefly, lungs were removed intact, degassed, and inflation-fixed for 24 hours at an intratracheal pressure of 25 cm H₂O with 10 percent neutral-buffered formalin. The lungs were sliced parasagittally at 1-cm intervals, and stratified random sections were taken, using a template. Sections were embedded in paraffin, cut at 6 micra and stained with hematoxylin and eosin. Mean linear intercept (Lm) and internal surface area (ISA) were measured from ten randomly chosen blocks. All small airways (SA) (defined as ≤2-mm diameter nonrespiratory bronchioles without alveoli or cartilage) were...
Table 1—Pulmonary Function in Two Adolescents with α1-Antitrypsin Deficiency

<table>
<thead>
<tr>
<th>Age. yr</th>
<th>TLC †</th>
<th>FVC †</th>
<th>RV/TLC †</th>
<th>FEV †</th>
<th>FEF 25-75 †</th>
<th>FEF 50 †</th>
<th>FEF 75 †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.4</td>
<td>115</td>
<td>97</td>
<td>35</td>
<td>80</td>
<td>74</td>
<td>—</td>
<td>55</td>
</tr>
<tr>
<td>14.1</td>
<td>111</td>
<td>81</td>
<td>43</td>
<td>71</td>
<td>62</td>
<td>—</td>
<td>44</td>
</tr>
<tr>
<td>15.2</td>
<td>108</td>
<td>94</td>
<td>29</td>
<td>77</td>
<td>58</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.3</td>
<td>98</td>
<td>81</td>
<td>34</td>
<td>75</td>
<td>69</td>
<td>—</td>
<td>52</td>
</tr>
<tr>
<td>12.9</td>
<td>95</td>
<td>80</td>
<td>38</td>
<td>72</td>
<td>64</td>
<td>—</td>
<td>64</td>
</tr>
<tr>
<td>14.0</td>
<td>80</td>
<td>77</td>
<td>24</td>
<td>70</td>
<td>58</td>
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<td>43</td>
</tr>
<tr>
<td>15.5</td>
<td>80</td>
<td>74</td>
<td>38</td>
<td>73</td>
<td>65</td>
<td>66</td>
<td>48</td>
</tr>
<tr>
<td>16.0</td>
<td>82</td>
<td>76</td>
<td>28</td>
<td>74</td>
<td>61</td>
<td>75</td>
<td>57</td>
</tr>
</tbody>
</table>

†TLC = total lung capacity; FVC = forced vital capacity; RV = residual volume; FEV = forced expiratory volume in one second; FEF 25-75% = forced expiratory flow between 25% and 75% of vital capacity; FEF 50% = forced expiratory flow at 50% of vital capacity; FEF 75% = forced expiratory flow after 75% of vital capacity has been expired. Percent predicted values based on height.13

marked, counted, and their internal diameters measured. Morphometric measurements were not made on case 1’s lungs, since they were not fixed under constant pressure. Both patients’ lungs were examined by standard histologic techniques, and in both cases the percentage of bronchial glands was quantitated by projection of transverse sections of the upper lobe, lingula or middle lobe and basilar trunk bronchi on a point-counting grid. The lungs of three 18-year-old males who died suddenly without respiratory disease or symptoms were used as controls and studied similarly.

RESULTS

Serial PFT results are presented in Table 1. Both cases had decreased flows at lower lung volumes (FEV 25-75%, FEF 50%, and FEF 75%) and slightly increased RV/TLC ratios. Lung function did not change significantly over the two-to-four-year follow-up period for either subject.

Diastase-resistant, PAS-positive cytoplasmic inclusions were present in hepatocytes of the cirrhotic livers of both patients, typical of those seen in liver disease related to the ZZ phenotype. Both patients also had membranoproliferative glomerulonephritis.

Grossly, even with examination of the lungs floating in water, no emphysema was evident. However, histologically, the lungs from both patients appeared to have slightly enlarged alveoli, particularly in the area of alveolar ducts (Fig 3A), when compared with the control lungs (Fig 3B). The dilation of these alveolar ducts was not accompanied by evidence of tissue destruction. Morphometric studies on case 2’s lungs showed an increase Lm, decreased ISA, and decreased specific ISA (Table 2). The total parenchymal volume of case 2’s lungs was 2,777 ml, while that of the three controls was 4,251 ± 713 ml. This small lung volume may reflect the patient’s chronic illness, since he weighed 33 kg (height 172 cm) at death.

The percentage of bronchial glands in case 2 was 21.3 percent and in case 1 15.3 percent. The mean value for two control subjects of similar age was 8.9 percent. Mean small airway diameter in case 2 was 0.78 ± 0.33 mm, compared with 0.67 ± 0.12 for controls. Both the density of small airways and the percentage of small airways less than 0.35 mm were within normal limits. Thus, there was no evidence of small airway stenosis.

By routine histologic examination, the lungs of both patients showed an acute bronchopneumonia, which in case 1 was hemorrhagic. Small airway inflammation was largely neutrophilic without any definite chronic small airway inflammation. No bronchiectasis was present. Small muscular arteries showed muscular thickening. Neither hemangiomata nor pulmonary arteriovenous fistulas were evident in the lungs or on the pleural surface in either subject, although special

Figure 3A (upper). Photomicrograph of case 2’s lung, alveolar ducts dilated and alveolar septa shortened (hematoxylin and eosin, × 51).

3B (lower). Photomicrograph of control lung at same magnification of Figure 3A (hematoxylin and eosin, × 51).
Table 2—Lung Morphometry in an α1-Antitrypsin-Deficient Patient

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lm, *μm</th>
<th>ISA, m²</th>
<th>ISA₂₅, m²/L</th>
<th>dₐ, mm</th>
<th>%SA &lt; .35, mm</th>
<th>#SA/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 2 (male, 16 yr)</td>
<td>244</td>
<td>45.5</td>
<td>16.4</td>
<td>0.78 ± 0.33</td>
<td>11.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Controls: Mean ± SD for three 18-year-old males</td>
<td>198 ± 24</td>
<td>85.8 ± 10.3</td>
<td>20.4 ± 2</td>
<td>0.67 ± 0.12</td>
<td>13.8 ± 10.4</td>
<td>1.00 ± .56</td>
</tr>
</tbody>
</table>

*Lm = mean linear intercept; ISA = internal surface area; ISA₂₅ = specific internal surface area; dₐ = average diameter of small airways (≤2 mm); %SA = percent small airways; and #SA = number of small airways.

studies to demonstrate these shunts conclusively were not performed.

**DISCUSSION**

These patients presented the unique opportunity to follow serial pulmonary function tests and examine pathology in two adolescents with AAT deficiency. Previous pathologic descriptions of the lungs in homozygous AAT deficiency have been limited primarily to lungs of adults. Greenberg et al. studied the lungs of three adults between 37 and 47 years of age dying with homozygous AAT deficiency. The authors noted a basilar panacinar emphysema, bronchial gland enlargement, and normal small airways. All three of these patients were formerly heavy smokers. Panacinar emphysema is the usual pathologic finding in patients with homozygous AAT deficiency, but chronic bronchitis and bronchiectasis have also been noted. In the previously mentioned autopsy series, however, it is difficult to exclude the effect of smoking on the enlarged bronchial glands.

Several investigators have described the appearance of panacinar emphysema associated with homozygous AAT deficiency in children.11-13 They, however, have not performed morphometric studies, and have demonstrated minimal increase in alveolar size. The nature of the airspace enlargement in case 2 is unclear. This enlargement is unlikely to be simple hyperinflation, since in a study of chronic asthmatic patients with clinical and radiologic hyperinflation, the Lm following endobronchial formalin inflation under uniform pressure was increased only in the few asthmatic patients with microscopic and gross emphysema.14 However, case 2 had no definite tissue destruction or gross emphysema, preventing us from diagnosing actual emphysema. Possibly this airspace enlargement indicates injury to the pulmonary parenchymal elastic skeleton. Such a diffuse alteration of the elastic skeleton has been postulated to explain why trivial amounts of emphysema significantly alter lung compliance and morphometric alveolar diameter.15 Thus these changes may represent a mild or early form of what is believed to occur with overt emphysema associated with homozygous AAT deficiency.

The increased RV and decreased air flows at low lung volumes (FEF 75%) indicate mild obstructive lung disease involving primarily peripheral airways. Previous investigators11-13,16 have examined symptomatic adolescents with AAT deficiency and have found similar decreased flows and increased lung volumes, as well as increased airway resistance, suggesting peripheral airways disease or early emphysema.

The present cases did not show any bronchiectasis by visual inspection or gross quantitation. However, small airways appeared to be dilated slightly compared with controls, suggesting a mild degree of what might be termed bronchiectasis (Table 2). Such changes have been reported by Glasgow et al11 and are probably secondary to destruction of the elastic laminae in the walls of the airways. The report by Hostek et al14 describes bronchiectasis in a 10½-year-old child, but makes no mention of small airway abnormalities in the resected pulmonary tissue. The bronchial gland enlargement, in the absence of a history of smoking, may reflect the response to repeated infections or an abnormal response to common airborne pollutants.

We did not do special studies to identify arteriovenous shunts within the lungs from these patients. However, Berthelot and coworkers17 discovered fistulas by injection studies on autopsy lungs from patients with similar liver disease. They also commented on the frequent finding of peripheral angiomas (as were observed in our patients), but did not mention any deaths from ruptured cerebral vessels. We were unable to find any previous reports of death from brain abscess in AAT-deficient patients with cirrhosis, although similar complications are reported in non-AAT-deficient patients with pulmonary arteriovenous fistulas.18 The severe hypoxia in both of our patients appeared to be due to pulmonary arteriovenous shunts and not to the mild obstructive lung disease.

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ACCP Postgraduate Course: 13th Annual
Pulmonary Nurse and Therapist Course—Pulmonary Rehabilitation and Home Care for Patients with COPD

This course, sponsored by the American College of Chest Physicians, the Pulmonary Division of the University of Colorado Health Sciences Center, Veterans Administration Medical Center of Denver, and the American Lung Association of Colorado, will be held April 17-22 at the Landmark Inn, Denver. Louise M. Nett, R.N., RRT, is course director. This pulmonary rehabilitation course is directed at the therapist or nurse responsible for a hospital-directed rehabilitation or home care program. A limited number of individuals not involved in a hospital-based program will be accepted. Speakers will focus on the role of the respiratory nurse and therapist in providing care to patients with chronic lung disease. A special "mini-management" session has been incorporated for management personnel interested in a general overview of pulmonary rehabilitation but not interested in details. The instructor for this session is a special consultant to hospital management staff. Tours will be arranged for those interested in visiting the Lutheran, University, or Rose Medical Center Hospitals' rehabilitation programs.


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