Familial Occurrence of Congenital Pulmonary Lymphangiectasis

Genetic Implications

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Congenital pulmonary lymphangiectasis (CPL) is a rare, generalized disease of the lung, consisting of lymphatic cysts in the subpleural and interlobular connective tissue. This disorder typically manifests a clinical picture of acute respiratory distress with cyanosis shortly after birth, with death occurring in the neonatal period. Several cases of this disorder have been described in the literature, but there has been no family with more than one affected child. We report the first instance, to our knowledge, of familial cases of CPL, which raises an important question regarding a possible genetic component in this disorder. The implications of this are discussed.


Congenital pulmonary lymphangiectasis was first recognized in 1856 by Virchow, and numerous reports of this disorder are found in the literature. Although the pathologic features of congenital pulmonary lymphangiectasis have been well delineated, the basic etiologic features have remained elusive.

Laurence developed a theory, based on histologic observations, that the primary developmental error is a loss of mitotic regulation in the lymphatic tissue of the developing lungs at about 16 weeks' gestation. This explanation, based on an error in control over cell division, suggests an abnormal event occurring at the molecular level of the cell and would imply some genetic component being present in congenital pulmonary lymphangiectasis. All cases thus far reported have been sporadic, with no mention of any form of familial clustering. We report the first documented instance, to our knowledge, of congenital pulmonary lymphangiectasis occurring in siblings.

**REPORT OF CASES**

The two children described herein and a normal female sibling were born to healthy parents. An extended family history was unremarkable, with no evidence of consanguinity. The mother, aged 17 years at the birth of patient 1, had no history of pregnancy wastage or exposure to any unusual environmental agents. The father, aged 20 years, was occasionally exposed to cleaning solvents through his occupation as an electrical technician.

Case 1. A full-term, 3,500-g, female infant was the first child of the parents. The prenatal course and delivery were uneventful. Cyanosis was noted at birth, and an Apgar score of 8 was recorded at five minutes. Respiration became progressively more difficult and a chest roentgenogram revealed bilateral pneumothorax that was worse on the left side (Fig 1). All attempts at therapy proved unsuccessful. The infant was pronounced dead six hours after birth.

Autopsy showed a well-developed newborn with no external anomalies. Internal examination showed bilateral pneumothorax with subpleural cysts throughout both lungs. Bilateral pulmonary atelectasis was also noted. The liver and spleen were enlarged and edematous, but no cysts were observed. The heart and all other organs appeared normal.

Histologic examination of both lungs demonstrated the presence of multiple cystic spaces within the pulmonary septa, peribronchial septum, and subpleural con-
Congenital pulmonary lymphangiectasis has been divided into three classes based on clinical and histologic findings. The most commonly occurring form is characterized by early onset of symptoms and death within a few hours after birth, usually less than 24 hours. The cystic spaces are confined mostly to the lungs, though they may be found in other organs such as heart, pancreas, and kidneys. There are no cardiac anomalies in this type. In the second type, the cystic lesions are more generalized, involving organs like the intestines, but sparing the heart. Although this type is also lethal, affected persons may survive for weeks or even years. The third group includes those...
cases with pulmonary venous obstruction as the primary anomaly. These individuals have secondary dilation of the lymphatics as postulated by Shortland-Webb et al.8

The two patients described herein exhibited features consistent with the first classification. The observation of pneumothorax, which occurred in both cases, has been described only once in association with congenital pulmonary lymphangiectasis.9 It is also important to note that this condition is quite distinct histologically from peripheral pulmonary cystic disease, which has been reported in siblings.9,10 In peripheral pulmonary cystic disease, the epithelial lining of the cysts is sometimes cuboidal rather than endothelial as in the cases reported herein. In our cases, the cysts were filled with fluid rather than consisting of air spaces that mostly occur in peripheral pulmonary cystic disease. The cysts in our cases were subpleural in location with close proximity to pulmonary vasculature, which is not usually the case in peripheral pulmonary cysts. Finally, peripheral pulmonary cystic disease is rarely fatal in the neonatal period as was the situation in our two cases. Therefore, we were clearly dealing with congenital pulmonary lymphangiectasis and not peripheral pulmonary cysts.

Congenital pulmonary lymphangiectasis has long been considered nonfamilial. However, the occurrence in siblings, as reported herein, stimulates speculation regarding a genetic component in this disorder as well as appropriate risk values for families in which congenital pulmonary lymphangiectasis has occurred. The proposal by Laurence that defective prenatal control of lymphatic growth results in congenital pulmonary lymphangiectasis seems to suggest a genetic regulatory involvement. Although the finding of one familial instance of this condition does not prove genetic interaction, we believe the possibility exists. There is also the possibility, as some investigators believe,10,11 that congenital pulmonary lymphangiectasia is more common in neonates with respiratory distress than is actually realized. The potential underestimate of the incidence of congenital pulmonary lymphangiectasia may obscure familial clustering and hence its true genetic component.

In this family, recurrence risks in a range up to 25% had to be stated, as autosomal recessive inheritance could not be ruled out. However, it is hoped that by alerting pediatricians to the possibility of congenital pulmonary lymphangiectasia in newborns with respiratory distress, ascertainment of this condition will lead to more accurate recurrence risks.

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References