Congenital alveolar proteinosis caused by a novel mutation of the surfactant protein B gene and misalignment of lung vessels in consanguineous kindred infants

Abstract Congenital alveolar proteinosis and misalignment of lung vessels are rare disorders. We report on five infants of consanguineous kindred. All infants were delivered at term after uneventful pregnancies. Shortly after birth they developed respiratory failure and severe persistent pulmonary hypertension. All died despite intensive care. Lung tissue of two infants was studied. Histological examination revealed combination of alveolar proteinosis and misalignment of lung vessels in one patient, alveolar proteinosis in the other. Immunostaining demonstrated surfactant protein B (SP-B) deficiency in both patients' lungs. In a further sibling, analysis of broncho-alveolar lavage fluid showed decreased surfactant protein. PCR and direct sequence analysis of the SP-B gene revealed three novel mutations. One of them, a single base deletion, shifts the reading frame at amino acid 122 and creates a premature termination of translation in exon 6. No mature SP-B protein is produced.

Conclusion Surfactant protein B deficiency caused by mutations of the respective gene and misalignment of lung vessels can concur. Both diseases may have a pathogenetic factor in common.

Key words Congenital alveolar proteinosis · Surfactant protein-B deficiency · Misalignment of lung vessels · Newborn · Mutation

Abbreviations CAP congenital alveolar proteinosis · ECMO extracorporeal membrane oxygenation · MLV misalignment of lung vessels · PPHN persistent pulmonary hypertension of the newborn · SP-B surfactant protein B
Introduction

Congenital alveolar proteinosis (CAP) and misalignment of lung vessels (MLV, also termed congenital alveolar capillary dysplasia) are rare disorders. Both diseases manifest in term neonates as severe respiratory distress and persistent pulmonary hypertension of the newborn (PPHN). The case fatality rate is high [5, 6, 7, 13, 14, 16, 18, 19].

In CAP alveoli are filled with granular protein-rich material, but lung structure is normal. In MLV pulmonary veins are anomalously related to bronchioles and pulmonary arteries, and alveoli are often dysplastic [5, 13, 19].

The aetiology of CAP could be elicited in some cases and is heterogeneous. Complete absence of surfactant protein B (SP-B) was recently demonstrated, and a mutation in the SP-B gene found [17]. In other cases of CAP, a granulocyte-macrophage colony stimulating factor (GM-CSF) receptor defect has been demonstrated [10].

MLV is considered a developmental disorder. Familial occurrence has been described [3], but a genetic defect is not known. Concurrence of MLV and CAP (due to SP-B deficiency) has to our knowledge not been described before.

Patients and methods

We report on five infants (referred to as A, B, C, D and E) born into a large kindred of kurdish descent with at least five consanguineous marriages (Fig. 1). All infants were delivered at term after uneventful pregnancies, developed respiratory failure and severe PPHN shortly after birth and expired despite intensive care. Lung tissue was studied in two infants (B and D). In a further infant (E) broncho-alveolar lavage fluid was analysed. In this patient and in family members who were available and consented (marked by an asterisk in Fig. 1) lymphocytes were harvested, DNA was extracted and amplified by PCR. PCR products were sequenced in infant E and his parents. All family members available were genotyped for the novel mutation 122delT using a PCR-based restriction fragment length polymorphism technique. Methods and results of the molecular genetic studies have been reported elsewhere in detail [15]. Here we report clinical, histological and, briefly, molecular genetic data of the patients, focussing on the concurrence of SP-B deficiency and MLV.

Clinical data of infants A and C, who had no histological or molecular genetic studies performed, are summarized in Table 1 with the data of infants B, D and E.

Case reports

Case 1

A boy (infant B) was born at 41 weeks gestation by Caesarian section to a 39-year-old healthy 16 gravida. The parents were first degree cousins (see Fig. 1). Five brothers and three sisters were healthy, six other boys (one of them infant A) and one girl had died in the 1st month of life. The baby developed severe respiratory distress requiring artificial ventilation with 100% oxygen. Results of diagnostic studies are shown in Table 1. Two doses of surfactant (Survanta, Abbott, North Chicago, Ill., USA) were given, with only short-term improvement. Epoprostenol was given continuously with some effect. The initial blood culture grew z-haemolytic streptococci. C-reactive protein increased to 6.0 mg/dl (normal <0.6 mg/dl). Immunoglobulin M was not elevated, and further virological or serological studies were not undertaken. The baby died on his 15th day of life in respiratory failure.

Fig. 1 Pedigree of family with cases of alveolar proteinosis, surfactant protein B deficiency, and misalignment of lung vessels. Roman numeral represent generation. Arab numeral represent number of individuals of same sex. Letter refer to case report.