Annotation

Surfactant apoprotein B deficiency

Fatal respiratory distress in term infants is rare and possible causes include persistent fetal circulation, meconium aspiration syndrome, pneumonia or congenital heart and lung abnormalities. Congenital pulmonary alveolar proteinosis has been described in several term newborns with respiratory failure. This diagnosis is determined by the characteristic histological appearance of the lung which is similar to that of the alveolar proteinosis observed in older children and adults. This condition results in an alveolitis of varying severity. Although infectious organisms including *Pneumocystis* and immunological defects have occasionally been implicated, the precise aetiology is unknown. A genetic basis for the congenital form has been suggested as its occurrence has been described in multiple siblings within several affected families. This possible genetic link was confirmed recently by the description of two term siblings with lethal respiratory failure and histopathological features of congenital alveolar proteinosis. Analysis of their lung tissue by immunological and molecular biological methods indicated an absence of one of the surfactant specific proteins, surfactant protein-B (SP-B), and its messenger RNA. Further cases of SP-B deficiency and lethal respiratory distress in newborns have since been described including three families in the United Kingdom, and a mutation of the SP-B gene has recently been recognised and described. This important development defines the mechanism for a condition that has been the subject of speculation for neonatologists over many years: inherited surfactant deficiency.

Human pulmonary surfactant is a mixture of 90% phospholipids and 10% proteins. Four surfactant associated proteins (apoproteins) have been identified: SP-A, SP-B, SP-C, and SP-D. Surfactant protein A is a hydrophilic protein and participates in the formation of tubular myelin, an intermediate form of surfactant. SP-A also has an important role in host defence along with surfactant protein D. Surfactant protein C is hydrophobic and enhances the rate of adsorption of phospholipids to the surface monolayer. Deleterious genetic aberrations of proteins A, C, and D are not known at present; some may be lethal in neonates but there may well be others that contribute to clinical pulmonary disease and that await discovery. The remainder of the article will focus on surfactant protein B and its absence.

Molecular and physiological properties of surfactant protein B

Surfactant protein B is expressed in two types of cell in the lung: type II pneumocytes and Clara cells. The 9.5 Kb gene encoding for SP-B is located on chromosome 2 and includes 11 exons. The 42 kDa proprotein transcript of this gene is processed within the endoplasmic reticulum and Golgi apparatus to the 8 kDa final peptide containing 79 amino acids within the Lamellar bodies. Lamellar bodies are the final compartment of intracellular pulmonary surfactant assembly before exocytosis and secretion into the alveolar space as part of tubular myelin, the framework for the surface active phospholipid monolayer of the air-liquid interface in the alveolus. Glucocorticoid receptors have been identified in the promoter region of the SP-B gene and have been shown to increase expression of SP-B in fetal lung both in vitro and in vivo by enhanced transcription and increased SP-B mRNA stability. The function of SP-B in Clara cells is not understood.

SP-B is hydrophobic and enhances the rate of adsorption of phospholipids into the surface monolayer. In vitro reconstitution experiments have suggested that SP-B is necessary for formation of tubular myelin. The intratracheal administration of monoclonal antibodies to SP-B in ventilated rabbits reduces lung compliance. Histological examination showed accumulation of amorphous proteinaceous material in terminal air spaces, desquamation of airways epithelium, and alveolar hyaline membranes.

Clinical features of surfactant protein B deficiency

The incidence and gene frequency of congenital SP-B deficiency is unknown. The inheritance is autosomal recessive. Thirty two patients have been identified and reported to date from North America and Europe. The British experience includes five newborns in three families. Two of these families were of Asian origin and the infants the product of a consanguineous marriage. All reported cases have been described in mature infants, although prematurity does not exclude the possibility of this diagnosis. A family history of previously affected infants may be elicited. All affected newborns develop respiratory distress within the first day of life. The rate of progression of disease and deterioration of respiratory function is variable but death is inevitable within the first
few months of life. Radiographic examination of the chest in most of them reveals a typical picture of respiratory distress syndrome, although the pattern of interstitial fibrosis may subsequently be seen. The respiratory failure is refractory to mechanical ventilation, steroids, and extra-corporeal membrane oxygenation. Exogenous surfactants, synthetic or natural, may produce a transient effect but do not alter the course of this disease. To date three infants in North America have undergone lung transplantation and all have survived. The eldest two are now over 12 months and had normal pulmonary function at 1 year (personal communication, F Sessions Cole).

Pathological features
Histological examination of lung tissue from biopsy specimens or post mortem examination shows the characteristic changes of alveolar proteinosis with pronounced accumulation of lipid rich, periodic acid Schiff positive, eosinophilic, proteinaceous, granular material consisting of desquamated type II pneumocytes and foamy macrophages within the alveolar air spaces. Alveolar lining cells are prominent. There is hypertrophy of type II cells and interstitial fibrosis. Long term mechanical ventilation may alter the microscopic appearance of the lung tissue with little detectable proteinosis. Electron microscopic examination showing disorganised tubular myelin and Lamellar bodies within the air spaces confirms disrupted surfactant secretion.

Surfactant proteins may be analysed in tracheal aspirates or bronchoalveolar lavage specimens by an ELISA technique or by immunoblotting and on lung histological sections by immunostaining. In infants treated with natural surfactants containing surfactant proteins, analysis for surfactant protein B should be delayed for at least 72 hours. Undetectable concentrations of SP-B are diagnostic. Increased accumulation of pro-SP-C, a precursor of SP-C, and an aberrant form of SP-C frequently accompany SP-B deficiency. An abnormal distribution of SP-A with a reduction in type II cells and an increase in the alveolar lumen has also been described.

Molecular features
DNA analysis for mutations is available from peripheral white cells but can also be extracted from necropsy lung specimens. Sequence analysis for cDNA clones generated by reverse transcriptase-polymerase chain reaction performed on RNA extracted from lung tissue of affected infants shows a substitution of three bases (GAA) at position 375 of the SP-B cDNA, a mutation which disrupts codon 121. This mutation is referred to as 121 ins2 and is located in exon 4 of the SP-B gene. The net gain of two bases causes a frameshift and introduces a premature signal for termination of translation after codon 214. In 12 children in five families with homozygous 121 ins2 SP-B deficiency and in seven children in five families with a compound heterozygous deficiency, the 121 ins2 mutation in one allele and another mutation in the other allele have been identified to date. In a further three families this mutation was not found on either allele.

Since the recognition of SP-B protein deficiency and the 121 ins2 mutation, two interesting clinical sequences have been described. The first is an infant with SP-B deficiency and compound heterozygosity for the 121 ins2 mutation who lived longer and seemed to respond to glucocorticoid administration compared with infants homozygous to the 121 ins2 mutation. This suggests heterogeneity of clinical phenotype associated with different genotypes. The second case is a description of fatal respiratory failure in a term infant with congenital alveolar proteinosis but normal surfactant protein concentrations. This suggests that there may be a different molecular defect in the SP-B gene that alters SP-B protein function, dysfunctional SP-A or SP-C, or a defect unrelated to surfactant apoproteins. The complex mechanisms that govern surfactant protein production, regulation, and function are being unravelled and in the near future further mutations and new defects will be discovered.

Conclusions
Inherited surfactant protein deficiency is rare but the diagnosis has important implications. It should be considered in all term infants with unexplained severe respiratory failure, particularly if they fail to improve within the first week of life. The only treatment at present is lung transplantation, but suitable donor organs are scarce, the procedure has considerable morbidity, and long term outcome is unknown. Compassionate withdrawal of intensive care may be more appropriate. Genetic counselling can be offered to families and if the infant is homozygous for the common mutation, antenatal diagnosis is possible with future pregnancies. Transfection of the human SP-B gene into rabbit lung endothelium using an adenovirus vector has been demonstrated, and this disease may provide a model for the development of gene therapy in the future.

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