

ATP-binding Cassette Transporter A3 (ABCA3) Mutation in a Late Preterm with Respiratory Distress Syndrome

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Background: Surfactant protein abnormalities are rare causes of respiratory distress syndrome. **Case characteristics:** A late preterm (36 wks) who presented with respiratory distress syndrome. **Observation:** He was found to be a homozygous for a G to T transversion at the first base in intron 24, of ABCA3 gene which is necessary for lamellar body formation and surfactant production. **Outcome:** He died of severe respiratory failure even after multiple doses of surfactants and ventilation. **Message:** Surfactant deficiency with ABCA3 gene mutation needs to be suspected in late preterms who present with respiratory distress syndrome.

Keywords: Neonate, Surfactant, Ventilation.

Inherited disorders of surfactant metabolism are rare causes of respiratory disease in newborns but are associated with significant morbidity and mortality. Severe neonatal lung disease is well known with SP-B protein gene mutation; SP-C deficiency is generally less severe and genetic disease related to SP-A and SRD are not yet reported [1]. Since the initial description of ABCA3 gene mutation in term infants with fatal surfactant deficiency, only few cases are reported till date. ABCA3 protein has been found in the limiting membrane of lamellar bodies of alveolar type II cells in the lungs and seems to be important for the formation of lamellar bodies and surfactant production. Although the precise incidences of these disorders are unknown, ABCA3 mutations appear to be the most common cause of inborn errors of surfactant metabolism [2]. We present a late preterm neonate, who was unsuccessfully treated with multiple doses of surfactant, and was later found to have a novel ABCA3 gene mutation.

CASE REPORT

A male neonate born vaginally at 36 weeks (birth weight 2250 g) to 26-year-old mother, developed respiratory distress by six hours of age.

He was a product of consanguineous marriage and the previous sibling had died of respiratory distress on 5th day of life. For the initial 24 hours he was managed with continuous positive airway pressure (CPAP) but in view of increasing respiratory distress and bilateral diffuse reticulogranular pattern in chest X-ray, he was ventilated. He received two doses of surfactant 12 hours apart at referring hospital but in view of high ventilatory pressure requirements (PIP- 26, PEEP- 6, Rate- 60 and FiO₂ of 100%), he was referred to us. On 8th day of life, baby received 3rd dose of surfactant in our hospital, which did not result in improvement of his condition. Subsequently

he was shifted on high frequency oscillatory, ventilation (HFOV) and an additional dose of surfactant. Brief period of improvement in ventilatory requirement and oxygenation was noted after surfactant administration every time. Other causes of respiratory distress like pulmonary hypertension, heart disease, infection, cystic fibrosis and any obvious lung malformation were excluded. With the above clinical setting, a diagnosis of congenital surfactant deficiency was considered.

Bronchoalveolar lavage was done to test for SP-B and C, and blood sample was collected for DNA analysis. Infant's condition deteriorated subsequently and he died on 39th day of life. Post-mortem lung biopsy was sent for histopathological study. Enzyme-linked immunosorbent assay (ELISA) using different monoclonal antibodies (done at John Hopkins laboratory, Baltimore, USA) showed adequate SP-A protein but SP-B protein was not detected. Immune staining for the surfactant proteins SP-B, ProSP-B, ProSP-C showed normal protein concentrations but there was absence of immunostaining of ABCA3 protein even at higher concentration of antibody. Lung biopsy revealed extremely thickened interstitium with histology of pseudoglandular lung.

Automated DNA sequencing was performed on both strands with the use of ABI Big Dye Terminator sequencing reagents and an ABI 3730 sequencer (Applied Biosystems). DNA sequencing was analyzed with the aid of Seq Man software (DNA Star) and Mutation Explorer software (Soft Genetics) which showed that infant was homozygous for a G to T transversion at the 1st base in intron 24 (immediately after exon 24). This could be referred as IVS 24+1 G>T or c3703+1 G>T, where 3703 refers to the numbering of the mRNA sequence and position 3703 corresponds to the last base in exon 24. No mutations were detected for

SP-B or SP-C gene. Genetic counseling and tests were offered to both parents but was refused. Antenatal study in next pregnancy showed normal surfactant protein level by ELISA test and a term male infant was born who was asymptomatic till one year of follow-up.

DISCUSSION

ABCA3 deficiency is increasingly being recognized as a cause of respiratory distress syndrome (RDS) in term babies in whom congenital deficiencies of SP-B and SP-C have been excluded. *ABCA3* gene is located on chromosome 16(16p13.3), spans more than 80kb bases, and contains 33 coding exons which encode a 1704 amino acid protein [2]. More than 180 distinct *ABCA3* gene mutations including missense, nonsense, splice site, frame shift, insertions and deletions have been detected 'private' and unique to a given family [1,3]. Lung disease caused by *ABCA3* mutation is inherited as an autosomal recessive disorder requiring mutations on both alleles. Depending on location of mutations in *ABCA3* gene, lung disease may be caused by loss or decreased expression of abnormal intracellular trafficking of the protein to the lamellar body, abnormal folding, packaging or secretion of phospholipids. It may also secondarily affect SP-B and SP-C processing [4].

Neonates who have *ABCA3* deficiency may present similarly as SP-B deficiency, with signs and symptoms of respiratory distress, pulmonary hypertension, diffuse infiltrates in X-ray, rapid progression to hypoxemic respiratory failure and death despite intensive medical therapy. The clinical course of babies with *ABCA3* deficiency varies from presentation in neonatal period to that in childhood presenting as interstitial lung disease. A common mutation involving substitution of valine for

glutamic acid in codon 292(E292V), of the *ABCA3* protein, has been identified in older children with chronic interstitial lung disease [1].

Detailed evaluation with immune staining, lung histology and gene sequencing showed evidence of a novel *ABCA3* gene mutation in this neonate whose clinical presentation was consistent with surfactant deficiency. Presence of this mutation in both allele could have accounted for the severity of disease in this neonate. Reduced amount of SP-B seen in our case could be explained by impaired processing of proSP-B to mature SP-B – that has been sometimes observed in association with *ABCA3* deficiency.

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