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A Novel Mutation (c.705C>A (p.C235*) (p.Cys235Ter)) in the SFTPB Gene That Causes Severe Respiratory Failure in A Term Newborn

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Abstract

Surfactants are surface-active agents lowering surface tension in the airways of the lung. It plays an important role on pulmonary function. Surfactant proteins constitute 10 percent of the surfactant molecule. Mutations in genes encoding surfactant proteins can be fatal. Surfactant protein B (SFTPB) gene mutation accounts for 50 percent of the cases that underwent lung transplantation for the treatment of severe respiratory failure due to surfactant protein gene mutations in infancy. More than 100 mutations in the surfactant protein B gene have been described. Variants in SPTPB cause pulmonary disease and due to production of insufficient amount and/or functionally abnormal surfactant, resulting in restrictive pathophysiology, with lungs that are poorly compliant and prone to atelectasis and low lung volumes. Here, we present a case of a term newborn who was referred with the diagnosis of persistent pulmonary hypertension of the newborn, who died due to a previously unidentified surfactant protein B gene mutation with severe respiratory failure and air leak syndromes.

Keywords

Novel mutation, Surfactant protein B gene, Severe respiratory failure, Term newborn

1. Introduction

Surfactant is a lipid-protein complex that regulates surface tension in the airways. It is one of the structures that play an important role in lung development and respiratory function [1, 2]. With the surfactant molecule, air-fluid contact at the alveolar surface is optimally provided. Surfactant deficiency is one of the most common causes of respiratory distress in neonates, especially in preterm infants. Phospholipid components account for approximately 90% by weight of pulmonary surfactant, of which 70-80% is phosphatidylcholine. The surfactant proteins play an important role in pulmonary surfactant function [3]. The protein components account for about 10% by weight of the pulmonary surfactant. Half of this consists of four surfactant-associated proteins, surfactant proteins A, B, C, and D (SP -A, SP -B, SP -C, and SP -D). SP -A and SP -D are involved in host defense in the lung, while SP -B and SP -C contribute to lowering the surface tension of pulmonary surfactant [4, 5]. Deficiency of SP -B is an autosomal recessive inherited disorder that occurs in approximately 1 per million live births and has been found in various racial and ethnic groups [6]. The SP -B gene is approximately 10 kilobases (kb) long, has been localized to human chromosome 2, and encodes a 381 amino acid long proprotein that is glycosylated and undergoes a series of proteolytic cleavages to form the 79 amino acid long, hydrophobic mature SP -B protein [7,8]. Over 30 loss-of- function recessive mutations and a total of 112 variations in SP -B have been identified, resulting in partial or complete

absence of the SP -B protein [9]. The most common mutation, a GAA substitution for C in codon 121, the '121ins2' mutation, is associated with approximately 70% of cases of SP -B deficiency and has a carrier frequency of 1 per 1,000 individuals [10]. The absence of SP -B results in a decreasing level of phosphatidylglycerol and an incomplete presence of SP -C, which has been shown to inhibit surfactant function in vitro [11, 12]. The absence of SP -B and the presence of this abnormal surfactant composition results in significant surfactant dysfunction, which contributes to the clinical syndrome.

Here, we describe a previously unidentified surfactant protein b gene mutation and the clinical features of the patient in a neonate with respiratory failure and persistent pulmonary hypertension of the newborn.

2. Case

A newborn was transferred to our tertiary neonatal intensive care unit because of respiratory distress. The infant was born to a 19-year-old mother whose pregnancy was complicated by hypertension treated with alpha methyl-dopa, without other medical problems or substance abuse. As gravida 1, para 1 of a 19-year-old mother, the baby was born at 40 weeks and 3 days by cesarean section in an external center at 3020 grams. She had intermittent hypertension in her follow-up and pregnancy history. It was noted that there was a kinship between the mother and father and they were first cousins. Among the relatives of the mother and father, there was no case suggestive of chronic lung disease or interstitial lung disease in an infant or older child, or any case who had died in the neonatal period due to respiratory problems. There were no abnormalities in the relatives except for hearing impairment. The patient, whose general condition was poor, was admitted to the neonatal intensive care unit intubated. While the patient was ventilated with 100% oxygen, the Spo2 on the right hand was 75. The Spo2 of the measured foot was 55. The patient underwent a whole blood test, biochemical values, acute phase reactants (C-reactive protein, CRP), chest X-ray, blood gasses, and blood culture. After the initial examination and chest X-ray, 200 milligrams/kg of poractant alfa was administered intratracheally. Blood gas values on the admission of the patient showed mild metabolic acidosis. On initial examination, his vital signs were a blood pressure of 61/45 millimeters of mercury and a body temperature of 36.5 degrees Celsius. The oxygen requirement of the patient, who was intubated, was between 80 and 100 percent. The spo2 values, on the other hand, were between 80 and 100, with intermittent desaturation. There was no difference in blood pressure between the lower and upper extremities. Venous blood gas analysis revealed pH: 7.31, pco2: 34.5 mmHg, po2: 67.5 mmHg, Hgb: 15 gr/dl, lactate: 2 mmol/l Hco3:18 mmol/L, BE: -8 mmol/L. Chest X-ray taken on admission revealed findings suggestive of congenital pneumonia or respiratory distress syndrome (RDS) (Figure 1). On the first day, conventional ventilation was continued (SIMV+ PS mode, pressure limitation and tidal volume targeted ventilation. Echocardiographic examination showed severe pulmonary hypertension. The ventricles had normal width and balanced size. A small secundum ASD with a left-to-right shunt was noted. The interventricular septum was intact. First-degree tricuspid regurgitation was noted with a flow velocity of 4.30 m/s. The right and left ventricular outflow tracts were clear. Ductus, coarctation in suprasternal study were not seen. Left ventricular functions were normal. Thrombi, vegetations and pericardial effusions were not observed. Left and right coronary artery outflows were observed with the corresponding origin. The estimated pulmonary artery pressure calculated from TR was 78 mm Hg, which was accepted as suprasystemic pressure and severe pulmonary hypertension. The initial blood count and biochemical parameters revealed no abnormalities. Only CRP level was high (92 mgram/L, reference range 0 - 5mg/L). Due to the patient's current clinical and pulmonary findings and high acute phase reactants, congenital pneumonia was considered and antibiotic therapy was initiated. Optimal ventilation modalities for pulmonary hypertension were tried in our neonatal clinic. Later, on the second day of his hospitalization, the development of pneumopericardium was observed (Figure 2). Due to air leak syndrome, ventilation was changed from conventional ventilation to high-frequency ventilation (HFOV). The HF jet ventilation could not be used because it was not available. Acceptable blood gasses could be achieved in the first three to four days. Oxygen requirements could be reduced to 40 percent. His saturations were generally above 80 and 85. Optimal hemodynamics and urine output could be achieved. During this period, dobutamine for pulmonary hypertension and midazolam and fentanyl for sedo-analgesia were added to the ongoing treatment. After HFOV, the pneumopericardium regressed spontaneously (Figure 3). It was observed that intratracheal surfactant caused mild to moderate improvement in oxygen saturation. Since the oxygenation index calculated from the mean airway pressure, Fio2 and PaO2 (MAP *Fio2/PaO2) was above 20, inhaled nitric oxide was added to the treatment. Vasodilator drugs such as prostacyclin (PG I2, Ilomedin), milrinone, sildenafil, bosentan and magnesium were used to support the treatment of pulmonary hypertension. Steroids such as dexamethasone and drugs such as hydroxychloroquine, which have been shown to be beneficial in some studies, have also been added to treatment. However, no clinical

improvement was noted. Surfactant was administered to the patient 6 times during his hospitalization. The partial benefit was obtained with the surfactant applications. The oxygenation index increased to above 40 at regular intervals and extracorporeal membrane oxygenation (ECMO) was considered. However, transporting the patient under these conditions was quite risky. Since there was no ECMO center in the city, the patient could not be transported. Gradually, ventilator support was increased to maintain the patient's oxygen saturation and keep him alive. Pulmonary air leak syndrome was observed. Initially, pneumothorax was noted in the left hemithorax (Figure 4). Then a chest tube was placed. Later, subcutaneous emphysema occurred, which was first observed in the neck region and then all over the body (Figure 5). As a result, a chest drain was placed in the right thorax. The subcutaneous emphysema was so prominent that it was visible even around the venous system on the right arm on direct radiographs, which showed an image of air (Figure 6). Repeated echocardiographic studies showed that the pulmonary hypertension findings did not regress. Since the patient's clinical findings did not improve, a sample was taken to determine the mutation of the surfactant protein gene in the patient. An EDTA blood sample was drawn from the patient's peripheral blood for molecular genetic testing for surfactant protein mutations. The patient died of severe respiratory failure on day 32 of hospitalization while awaiting the results of the genetic analyzes. Whole gene sequencing was performed for the ABCA3, CSF2RA, CSF2RB, SFTPA1, SFTPB, SFTPC, and SFTPD genes, including all coding regions and exon-intron junction regions of the coding exons. This assay was performed using the next-generation sequencing method called Illumina - Miseq. Except for the surfactant protein B gene, no pathogenic features were found. A mutation was detected in the SFTPB gene (NM _198843.3) c.705C > A (p.C235*) (p.Cys235Ter) (homozygous). The alteration in the SFTPB gene detected in the analysis is a genetic alteration (novel mutation) that has not been previously reported in the literature in any other patient. However, the detected variant was considered highly likely to be pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria. Genetic counseling was recommended to reveal the carrier status related to this mutation, as the parents are very young and wish to have children again and have a healthy child with a preimplantation genetic diagnosis. This process is still ongoing, it is not finished yet.

3. Discussion

Herein, we present a case of severe respiratory failure resulting in death in a term newborn with a novel mutation in the SFTPB gene [(NM _198843.3) c.705C > A (p.C235*) (p.Cys235Ter) (homozygous)] that has not been previously described in the literature.

To date, more than 100 mutations have been described in genes encoding surfactant protein. Children and infants with genetic disorders of surfactant metabolism generally have 2 clinical presentations. One of these, the most dramatic, is severe respiratory failure requiring ventilatory support, which occurs in a term newborn shortly after birth. These cases usually respond minimally or transiently to surfactant substitution and these babies are very likely to require ECMO. Pulmonary hypertension observed may respond partially to inhaled nitric oxide. Typically, chest radiographs show similarities to RDS in observed preterm infants with diffuse opacification and air bronchograms. This acute clinical picture is typical of infants with loss-of-function mutations in SFTPB or ABCA3 but has also been observed in approximately 10% of infants with mutations in SFTPC [13-16]. In agreement with the literature, the typical chest radiographic findings and clinical findings in a term neonate whose clinical condition did not improve suggested that genetic disorders of surfactant metabolism might be present in this case. The presence of a homozygous mutation in the surfactant protein b gene in our patient is consistent with the literature.

Surfactant proteins have regulatory roles on lung infection and sepsis. In an animal study investigating the regulatory roles of human surfactant protein b variants on genetic susceptibility to Pseudomonas Aereginosa pneumonia and sepsis, it was shown that SFTPB variants affect susceptibility to sepsis through surfactant, cell apoptosis and inflammatory signaling in sepsis [19]. In this study, transgenic SFTPB mice exhibited inflammatory activation and higher activated caspase-3 in tissue specimen. Similar to the findings in this study, patients that have genetic disorders of surfactant metabolism, face morbidities related to mechanical ventilator and oxygen consumption to survive, as well as complications such as ventilator-associated pneumonia due to difficulties with weaning from the ventilator. In our patient, gram-negative colonization in tracheal aspirate cultures and gram-negative bacterial sepsis attacks were occasionally observed, consistent with the literature. In vitro studies in the treatment of surfactant protein b deficiency showed promising positive results via delivery of a lentiviral vector pseudotyped with Sendai virus glycoproteins F/HN expressing surfactant protein B [20].

Complete deficiency of SP -B leads to fatal neonatal respiratory disease [17]. The only curable treatment is lung transplantation. In a study investigating the outcomes of lung transplantation in infants and children with genetic

disorders of surfactant metabolism, a total of 28 patients less than 1 year of age underwent lung transplantation between 1993 and 2015 [18]. In this study, it was found that 50% of lung transplants performed in infancy, or 14 cases, were due to surfactant protein b gene mutations. When the cases that underwent lung transplantation in infancy were examined, it was found that the mean transplant age was 4.1 months in epoch 1 (1993-2003) and 5.6 months in epoch 2 (2004-2015). In the same study, the authors found that survival at age 1 year was 83% and at age 5 years was approximately 56%. Although transplantation may provide short-term survival in infants and children with otherwise fatal genetic lung disease, it is associated with chronic medical challenges and long-term morbidities.

4. Conclusion

The absence of risk factors for RDS or infection in an infant with diffuse parenchymal lung disease should raise suspicion of inherited surfactant metabolism disorders, and a family history of severe neonatal lung disease should prompt investigation. In particular, in cases in which there is no clinical improvement and the finding of pulmonary hypertension does not resolve and cannot be explained by any other cause, we should think of an inherited disorder of surfactant metabolism, especially in term or near-term babies. Apart from the fact that ECMO is difficult to access and transport in developing countries, lung transplantation for inherited disorders of surfactant metabolism is almost never performed in infancy. Therefore, it would be most prudent to avoid consanguineous marriages in developing countries or, if possible, to have healthy individuals with a preimplantation genetic diagnosis.

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