During a routine pediatric visit at 2 months of age, a female infant was noted to have poor weight gain and tachypnea with increased work of breathing. Her respiratory symptoms progressed and by the end of the week, she required admission to the hospital and mechanical ventilation. She was dependent on the ventilator for a prolonged period but then recovered and was discharged from the hospital at 5 months of age.

Two years later, the parents of this infant had a second female child who did not have any lung disease. However, their third child presented immediately after birth with severe hypoxemic respiratory failure from which he did not survive despite maximal therapy. Testing revealed that this infant had a similar protein deficiency as their first child, which was not present in their middle child or either parent.

Of the following, the MOST likely protein that is deficient in the two symptomatic siblings is:

A. ATP-binding cassette member A3
B. surfactant protein A
C. surfactant protein B
D. surfactant protein C
E. surfactant protein D

Surfactant deficiency may be attributable to decreased production because of pulmonary immaturity or as a result of genetic mechanisms that disrupt the production of critical proteins involved in surfactant function and metabolism. Although inherited surfactant deficiency disorders are rare, their associated morbidities and mortalities are high. At present, the most commonly known surfactant disorders result from deficiencies in the surfactant lipid-associated transporter known as adenosine triphosphate (ATP)–binding cassette member A3 (ABCA3), surfactant protein (SP)-B, or SP-C (Table). Disorders associated with these protein deficiencies have different inheritance patterns, variable onset and severity of clinical disease, and distinct pathogeneses.

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Genetics</th>
<th>Onset of Clinical Symptoms</th>
<th>Radiographic Similarity to RDS vs ILD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA3</td>
<td>Autosomal recessive</td>
<td>Neonatal period most common</td>
<td>RDS or ILD</td>
<td>Variable (typically lethal without transplant if presents in neonatal period)</td>
</tr>
<tr>
<td>SP-B</td>
<td>Autosomal</td>
<td>Neonatal period</td>
<td>RDS</td>
<td>Fatal without</td>
</tr>
</tbody>
</table>
Abnormalities in the production of surfactant protein B (SP-B), surfactant protein C (SP-C), and ABCA3 can lead to severe lung disease in infants. SP-B is essential for the formation of lamellar bodies, which are involved in the production of surfactant. Deficiency in SP-B leads to a decrease in the levels of phosphatidylcholine and phosphatidylglycerol, which are crucial for lowering alveolar surface tension.

Deficiency in SP-C results in the absence of SP-C protein, which is necessary for the proper function of surfactant. This leads to abnormal surfactant composition, characterized by decreased amounts of phosphatidylcholine and phosphatidylglycerol, and a lack of normal lamellar bodies, which are important for the formation of surfactant.

Deficiency in ABCA3 is also associated with severe lung disease. ABCA3 is involved in the transport of surfactant lipids, and mutations in this gene can lead to decreased surfactant function and a lack of normal lamellar bodies.

The severity of lung disease associated with these deficiencies can range from mild to severe, and can affect infants born at term or preterm. The clinical course can vary, with some infants presenting immediately after birth with respiratory distress syndrome and/or pulmonary hypertension, while others may appear healthy in the neonatal period.

The precise role of ABCA3 in surfactant metabolism is not completely understood. Infants deficient in ABCA3 lack desaturated phosphatidylcholine and phosphatidylglycerol, which have reduced surface tension-lowering ability, and possess few normal lamellar bodies. These findings suggest that ABCA3 is involved in lamellar body formation and surfactant function. The most likely protein that is deficient in the siblings in the vignette is ABCA3 because of the variability in clinical disease and timing of presentation, as well as an autosomal recessive pattern of inheritance.

At present, there are no known inherited mutations in the genes encoding SP-A. Genetically engineered SP-A-deficient mice do not develop any lung disease. However, these mice are more susceptible to bacterial and viral pathogens in the lung. This latter finding is not surprising given the role of SP-A in providing an innate host defense system to the lungs.

Surfactant protein B deficiency is an extremely rare autosomal recessive disorder with initial clinical manifestations similar to those of ABCA3 deficiency. Neonates with a complete deficiency of SP-B typically are born at full term and present with respiratory distress within a few hours. At presentation, the severity of symptoms and degree of lung disease is variable, with some infants having mild symptoms in the first few postnatal days, and others exhibiting a rapid onset of severe hypoxic respiratory failure requiring extracorporeal membrane oxygenation. Radiographic findings in all neonates correlate with surfactant deficiency observed in preterm infants.

Regardless of the initial clinical presentation and in contrast to infants with ABCA3 deficiency, all infants with SP-B deficiency have progressive disease, with transient improvement after surfactant administration and modest improvement with corticosteroid therapy. Infants typically die of respiratory failure within 3 to 6 months despite maximal medical therapy; at present, lung transplantation is the only effective therapeutic option. Although the third infant in the vignette had a clinical presentation and onset that could be consistent with SP-B deficiency, the initial onset of disease at 2 months of age with complete recovery in the first child is not consistent with a deficiency of SP-B.

Experiments in genetically engineered mice suggest that a critical level of SP-B expression is required for proper lung function. Indeed, some infants with partial deficiency of SP-B can survive beyond the neonatal period. However, in the presence of additional factors attenuating SP-B production, such as prematurity or inflammation, even infants with partial SP-B deficiency are at high risk of severe lung disease.

In addition to lacking SP-B protein with resultant inability to lower alveolar surface tension, infants with SP-B deficiency lack normal lamellar bodies, and instead have disorganized lamellated vesicular inclusions. This lack of normal lamellar body formation leads to altered phospholipid composition of surfactant with decreased amounts of phosphatidylcholine and phosphatidylglycerol. In addition, this lamellar abnormality may also contribute to the incomplete processing of the SP-C protein to the mature form. This lack of mature SP-C compounds creates a double effect, perhaps contributing to the lethality of SP-B deficiency in the immediate neonatal period.

In contrast to infants with SP-B or ABCA3 deficiency, infants affected by SP-C deficiency typically present after the neonatal period with an acute form presenting during infancy and a chronic form evident during adulthood. The severity of lung disease associated with SP-C gene mutations is highly variable, even among family members with the same genetic abnormality; this suggests that environmental and other genetic factors alter the pathogenesis of this disease. A radiographic pattern of interstitial lung disease is more common than respiratory distress syndrome. Unlike SP-B or ABCA3 deficiency, infants with SP-C deficiency can have a mutation on only one allele and this is typically inherited in an autosomal dominant pattern with some sporadic cases being reported. SP-C gene mutations lead to irregular folding of the precursor of SP-C, which is directly toxic to alveolar epithelial cells. Because SP-B protein is unaffected in SP-C-deficient infants, one explanation for the lack of perinatal disease in this group is that SP-B production can compensate for the absence of SP-C. The affected infants in the vignette are unlikely to have a deficiency of SP-C because neither parent is affected and the genetic pattern does not suggest an autosomal dominant inheritance.
Similar to SP-A–deficient mice, mice genetically engineered to lack SP-D expression do not have any perinatal disease. However, SP-D–deficient mice do develop lipid accumulation and emphysema with time. Although an inherited SP-D deficiency has not been identified in humans, infants with this deficiency would probably not present clinically in the neonatal period.

References


American Board of Pediatrics Content Specification(s)
Respiratory: Know the pathophysiology and risk factors for RDS
Respiratory: Recognize the pathologic features of RDS