

Surfactant Protein B Deficiency Caused by Homozygous C248X Mutation—A Case Report and Review of the Literature

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Am J Perinatol Rep 2015;5:e53–e59.

Abstract

Objective Surfactant protein B (SP-B) deficiency is a rare autosomal recessive disorder that is usually rapidly fatal. The c.397delCinsGAA mutation (121ins2) in exon 4 is found in more than two-thirds of patients.

Design We report on a fatal case of SP-B deficiency caused by a homozygous C248X mutation in exon 7 of the SP-B gene. In addition, we provide an update of the current literature. The EMBASE, MEDLINE, and CINAHL databases were systematically searched to identify all papers published in the English and German literature on SP-B deficiency between 1989 and 2013.

Results SP-B deficiency is characterized by progressive hypoxemic respiratory failure generally in full-term infants. They present with symptoms of respiratory distress and hypoxemia; chest X-ray resembles hyaline membrane disease. Prenatal diagnosis is possible from amniotic fluid or chorionic villi sampling.

Conclusion Thirty-four mutations have been published in the literature. Treatment options are scarce. Gene therapy is hoped to be an option in the future.

Keywords

- ▶ surfactant
- ▶ newborn infant
- ▶ respiratory distress
- ▶ surfactant protein B deficiency

Surfactant protein B (SP-B) deficiency is a rare disease with an estimated incidence of 1 in 1 million live births.^{1–3} Although the clinical picture initially varies in severity and symptoms, SP-B deficiency constitutes a progressive disorder that commonly presents as severe lung disease requiring mechanical ventilation and even cardiopulmonary bypass.^{4,5} Only transient and inconsistent responses to interventions including exogenous surfactant administration and high-dose corticosteroids have

been reported.⁴ Clinical and radiographic findings are consistent with respiratory distress syndrome in preterm born infants.^{6,7} At present, lung transplantation represents the only therapeutic option offering long-term survival.^{5,8,9} We searched the literature between 1989 and 2013 on SP-B deficiency using the EMBASE, MEDLINE, and CINAHL databases to provide data on published mutations and single-nucleotide polymorphisms (SNPs) as well as an overview on current

received
August 18, 2014
accepted after revision
December 23, 2014
published online
March 2, 2015

DOI <http://dx.doi.org/10.1055/s-0035-1545668>.
ISSN 2157-6998.

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knowledge regarding diagnosis and treatment. Further, we report on a case of a fatal SP-B deficient infant.

Case Report

We report on a male neonate of 40 weeks' gestational age and 3.260-g birth weight, born to a 41-year-old mother. Parents were Caucasian and not related. This was the second pregnancy that proceeded uneventful. Amniocentesis was performed showing a normal male karyotype. The boy was born by caesarean section and initially presented with a weak cry, shallow breathing, hypotonia, and peripheral cyanosis.

Following bag-mask ventilation for 1 minute, the infant's breathing improved and the skin turned rosy. Subsequently, nasal continuous positive airway pressure (CPAP) was initiated resulting in prompt adaptation. Apgar scores were 7/10/10 at 1/5/10 minutes, respectively. Body length (52 cm) and head circumference (35 cm) were within normal ranges. Within the first hours of life tachy- and dyspnea increased and oxygen demand was increasing (FiO_2 0.3–0.5), whereas auscultation was unremarkable. At the age of 4 hours the infant was transferred to the neonatal intensive care unit (NICU) presenting with tachypnea (RR 70/min), pale skin, expiratory wheezing, and respiratory distress. SpO_2 was 93% at FiO_2 of 0.3. Chest X-ray showed mild diffuse infiltrations in both lungs (► Fig. 1). Laboratory findings revealed respiratory acidosis ($PaCO_2$ 56 mm Hg). On the third day of life, mechanical ventilation was initiated because of worsened respiratory status, FiO_2 of 0.7, and $PaCO_2$ of 68 mm Hg. Chest X-ray revealed reduced lung volume and reticular infiltrations with positive air bronchogram. Surfactant replacement therapy (100 mg/kg body weight porcine surfactant [Curosurf, Chiesi Pharmaceuticals, Vienna, Austria]) resulted in acute improvement of oxygenation (reduction of FiO_2 to 0.4). However, within the following hours oxygen demand increased again. Within the first week of life FiO_2 ranged between 0.5 and 0.7. A 6-day course of methylprednisolone was unsuccessful. Congenital heart disease was excluded by echocardiography.

High-frequency oscillatory ventilation (HFOV) in combination with inhaled nitric oxide, as well as repeated surfactant supplementation and subsequent conventional mechanical ventilation, resulted in solely intermittent respiratory improvement and oxygen demand persisted at FiO_2 of 0.4 to 0.5. As far as surfactant dysfunction disorder was suspected, SP gene analysis from a blood sample was performed (University Hospital of Karlsruhe, Germany). Genetic analysis revealed SP-B deficiency caused by a homozygous C248X (p.Cys248Term, c.758C > A, TGC > TGA) mutation on exon 7 of the SP-B gene. Tracheotomy was performed at day 50 of life (see ► Fig. 2 showing chest X-ray). Lung transplant in case of worsening respiratory situation was declined by the parents. At the age of 92 days the boy died due to respiratory failure.

Parents declined further investigations regarding possible heterozygosity.

Surfactant: Components and Metabolism

Surfactant proteins (SPs) play an important role in metabolism, structure, and function of surfactant. Surfactant contains the four known surfactant associated proteins: SP-A, SP-B, SP-C, and SP-D, which are synthesized and secreted by alveolar type II cells and are classified into hydrophobic (SP-B and SP-C) and hydrophilic (SP-A and SP-D) proteins.¹⁰ SPs are well characterized regarding the respective genes, amino acid compositions, and messenger RNA (mRNA) sequences.^{10,11}

SP-B is a 79 amino acid protein. There is a single gene on the short arm of chromosome 2 (2p12-p11.2) responsible for encoding SP-B.^{10,12} SP-B is a hydrophobic protein comprising 2% of surfactant composition. It is secreted by type II epithelial cells as a large precursor protein (proSP-B). ProSP-B is split by proteolytic enzymes at the amino- and carboxyl-terminus, resulting in a smaller and extremely hydrophobic peptide.^{7,13,14} SP-B is synthesized in the endoplasmic reticulum. mRNA is translated into a 381 amino acid preproprotein, of which the first 23 amino acids comprise a signal peptide that is co-translationally removed.⁴ SP-B is transported



Fig. 1 Early chest X-ray.



Fig. 2 Chest X-ray after tracheotomy.

through the Golgi apparatus into multivesicular bodies. During this transport proteolytic processing of the precursor protein is initiated.¹⁵ The final processing occurs when the multivesicular bodies fuse with the lamellar body. At this stage packaging of the mature protein into surfactant phospholipid membranes takes place.¹⁰ Being stored in lamellar bodies, SP-B is then secreted into the alveolar lumen by exocytosis.^{10,16,17} Subsequently, the lamellar body converts to produce tubular myelin, which is converted into a lipid-rich film spreading along the alveolar surface at the air-liquid interface.^{10,18,19} SP-B enables the adsorption of the surfactant phospholipid film to the air-liquid interface and thereby contributes to the surface tension reducing capacity of surfactant. Furthermore, SP-B participates in the formation of tubular myelin.^{10,18-21} Recycling of surfactant phospholipids and proteins is performed by alveolar type II cells after endocytosis; alternatively, they are catabolized by alveolar macrophages. The expression of SP-B and other proteins involved in surfactant metabolism increases in late gestational age along with other aspects of lung maturation.¹⁰ During the last third of gestation immature glycogen-rich alveolar type II cells begin to mature, resulting in the disappearance of glycogen while surfactant production increases.²²

Genetics and Histopathology of SP-B Deficiency

SP-B deficiency is an autosomal recessive disorder. Carriers of only one mutation are usually asymptomatic.^{22,23} SP-B deficiency was first recognized in 1993 in a family with three full-term infants who died from fatal respiratory disease with clinical and radiologic findings mimicking surfactant deficiency.⁷ Complete lacking of SP-B in lung tissue was found, as well as undetectable levels of mRNA.⁷ Subsequently, affected children were found to be homozygous for a frameshift mutation being responsible for the lack of SP-B, constituting SP-B deficiency as basis of the infant's disease.¹⁴ The same mutation was also found in three other infants unrelated to those described earlier, who had died from similar lung disease. These findings indicated the mutation found to be relatively common for this disease. The mutation involves the substitution of three bases for one in exon 4 of the gene, corresponding to codon 121 of the SP-B mRNA, and has been termed 121ins2 mutation for the net two base-pair insertion.⁴ Current nomenclature for this mutation is c.397delCinsGAA according to DNA level.²⁴ This mutation results in extremely low levels of SP-B mRNA, caused by rapid degradation of the mutated mRNA lacking a polyadenylation sequence. **Table 1** shows currently known mutations in the SP-B gene bearing clinical relevance revealed by literature research.^{3,5,11,19,25-35} More than two-thirds of patients carry the c.397delCinsGAA mutation. The residual mutations include nonsense, missense, frameshift, and splice-site mutations, as well as insertions and deletions throughout the gene and a large deletion comprising exons 7 and 8.^{30,34} SP-B is detected in human fetal lung tissue (mRNA) as early as 12 weeks' gestation and in human amniotic fluid from 30 weeks' gestation onward. Mutations of the SP-B gene generally result in loss of function or even

complete absence of SP-B, causing acute respiratory distress in full-term infants. Respiratory distress is progressive and usually fatal at 3 to 6 months of age.⁵ Genetic counseling is important due to a recurrence risk of 25%.

From the histopathologic point of view, SP-B deficiency is associated with congenital pulmonary alveolar proteinosis (PAP) and, although less frequently, with infantile desquamative interstitial pneumonitis.^{10,36} These associations are based on the most characteristic histological feature of SP-B deficiency, which is the accumulation of granular, eosinophilic, periodic acid Schiff-positive, lipoproteinaceous material in the alveolar spaces, often containing desquamated alveolar type II cells and foamy alveolar macrophages.^{10,36} Histological findings of PAP in children caused by mutations in the common β or α subunit of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor differ to those in SP-B deficiency.^{10,37-39} Alveolar proteinosis material is found in large amounts in association with impaired GM-CSF function, whereas alveolar proteinosis material in SP-B deficient infants ranges from large amounts to even complete absence.¹⁰ Therefore, back in 1998 Nogee suggested that the term hereditary SP-B deficiency more accurately describes the condition than the term congenital alveolar proteinosis. Furthermore, hyperplastic alveolar epithelia with prominent type II cells and thickening of the alveolar walls, characterized by fibroblast proliferation including little to no inflammatory cell infiltrates, distinguishes SP-B deficiency from GM-CSF abnormalities.¹⁰ Hyperplastic alveolar epithelium interspersed with thickened interstitial septa does not only represent features consistent with impaired alveolar formation, but it may also reflect nonspecific changes in the tissue, eventually being caused by injury from prolonged mechanical ventilation and oxygen therapy.^{10,40}

Epidemiology

The population frequency of SP-B deficiency is currently unknown. However, an incidence of 1 in 1 million live births is estimated for the United States.¹ The c.397delCinsGAA (121ins2) mutation is represented by an allele frequency of 1 per 1,000 to 3,000 individuals.¹⁻³ However, SP-B deficiency constituting a very rare disease might be underdiagnosed due to phenotypic variability and lack of awareness.

Clinical Presentation

Affected infants present well right after birth, showing no symptoms that might lead to the suspicion of SP-B deficiency. Hours after birth infants develop symptoms of surfactant deficiency, including tachypnea, grunting, retractions, nasal flaring, increased oxygen demand, and gray pallor. Blood gas analysis shows acidosis, hypoxemia, and hypercarbia. Radiographic findings show reticulogranular patterns with positive air bronchogram, increasing lung opacification, and reduced lung volume.⁶

Respiratory failure is associated with the need for mechanical ventilation, HFOV, inhaled nitric oxide, or even extracorporeal membrane oxygenation (ECMO). However, these measures and surfactant replacement therapy result in only transient improvement of the respiratory condition.

Table 1 Mutations of clinical relevance in the SP-B gene published in the literature^{3,5,11,19,25–35}

| DNA level | Protein | AKA | Allele frequency, dbSNP | Exon | Type | Reference |
|--------------------------------------|------------------------------|------------------------------|---------------------------|----------|-------------------|----------------------------------|
| c.74T > C | <i>p.L25P</i> | T52C, (<i>L13P</i>) | nl | 1 | Miss | Nogee et al ⁵ |
| c.153G > A | <i>p.W51*</i> | [G441A], (<i>W39X</i>) | nl | 2 | Nons | Nogee et al ⁵ |
| c.169delC | | [457delC] | nl | 2 | Frame | Tredano et al ³² |
| c.181T > C | <i>p.C61R</i> | [T469C], (<i>C49R</i>) | nl | 2 | Miss | Nogee et al ⁵ |
| c.208delG | | [496delG] | nl | 2 | Frame | Tredano et al ³ |
| c.216G > A | <i>p.W72*</i> | [G504A], (<i>W60X</i>) | nl | 2 | Nons | Nogee et al ³ |
| IVS2 + 4A > G | | 209 + 4A > G | nl | 2 | Splice | Nogee et al ⁵ |
| c.304–2delA | | 282–2delA | nl | | Splice | Nogee et al ⁵ |
| c.334T > G | <i>p.C112G</i> | [T1486G], (<i>C100G</i>) | nl | 4 | Miss | Nogee et al ⁵ |
| c.397delCinsGAA | | 121ins2 | nl rs35328240 | 4 | Frame | Nogee et al ⁵ |
| c.400delC | | [1552delC], 122delC | nl | 4 | Frame | Somaschini et al ³¹ |
| c.401delT | | [1553delT], 122delT | nl | 4 | Frame | Lin et al ²⁹ |
| c.412delT | | 379delT | nl | | | Nogee et al ⁵ |
| | <i>p.I143T</i> c.428T > C | [T1580C] | 0.5039 rs1130866 | 4 | Miss DP | Tredano et al ³³ |
| c.436_437dupAA | | [2415–2416insAA] | nl | 5 | Frame | Williams et al ³⁵ |
| c.439G > A | <i>p.G147S</i> | [G2417A], (<i>G135S</i>) | 0.001849 rs35373464 | 5 | Miss | Klein et al ²⁸ |
| c.501G > T | | [G2479T] | nl | 5 | Splice | Dunbar et al ²⁶ |
| c.718G > A | | [G2913A], IVS6 as G-A +10 | nl | 6 | Splice | Nogee et al ⁵ |
| c.739T > C | <i>p.C247R</i> | T717C (<i>R235R</i>) | 0.00001829 | 7 | Miss | Nogee et al ⁵ |
| c.742C > T | <i>p.R248C</i> | [C4380T], (<i>R236C</i>) | 0.00005474 rs137853202 | 7 | Miss | Ballard et al ²⁵ |
| c.780C > A | <i>p.C260*</i> | C758A (<i>C248X</i>) | 0.00004056 | 7 | Nons | Nogee et al ⁵ |
| c.790C > T | <i>p.R264C</i> | C768T (<i>R252C</i>) | nl | 7 | Miss | Nogee et al ⁵ |
| 4729–4730ins18 | | | | 8 | InFrame ins | Wenger et al ³⁴ |
| c.1069_1070insCGC | | 1043ins3 | nl | 9 | InFrame ins | Nogee et al ⁵ |
| c.1070_1081del12 | | 1048del12 | nl | 9 | InFrame del | Nogee et al ⁵ |
| Deletion of 2958 bp incl. ex. 7–8 | | | nl | 7–8 | Gross deletion | Weaver et al ¹¹ |
| c.673–1248del2959 incl. ex. 7–8 | | | nl | 7–8 | Gross deletion | Schuerman et al ³⁰ |
| 1970insdel(CA)n | | | nl | Intron 4 | Other | Floros et al ²⁷ |

Abbreviations: AKA, also known as; DP, disease-associated polymorphism; Frame, Frameshift insertion/deletion; InFrame del, In-frame deletion; InFrame ins, In-frame insertion; Miss, Missense, nl, not listed; Nons, nonsense; SP-B, surfactant protein B.

Note: First column DNA level corresponding with HGMD database, NM_198843.2; second column protein referring to XP_005264544.1; fourth column Allele frequency according to Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: <http://exac.broadinstitute.org>) [12, 2014] and.¹⁹

In contrast, very few infants appear to have milder respiratory symptoms, with chest X-rays and clinical picture being consistent with more benign diagnoses such as transient tachypnea of the newborn.⁵ Milder disease allowing prolonged survival has been observed in few children with mutations that allow for some residual SP-B production, and has been termed partial SP-B deficiency.²⁶ Data of 23

infants with diagnosis of SP-B deficiency from the literature are displayed in **Table 2**.^{7,8,13,28,31,35,41–47} Because not all infants reported in the literature are found as full case reports including baseline demographic data and precise clinical course or underlying mutation of the SP-B gene, it is not possible to present all these data in this table for each individual case.

Table 2 Data on 23 infants with SP-B deficiency reported from the literature^{7,8,13,28,31,35,41–47}

| | |
|---|------------|
| Consanguinity | 7/11 (64) |
| Male gender | 11/20 (55) |
| Signs of RDS within hours after birth | 23 (100) |
| Mechanical ventilation | 21/23 (91) |
| Surfactant | 16/22 (73) |
| Improvement after surfactant administration | 15/22 (68) |
| HFO | 7 (30) |
| NO | 4 (17) |
| ECMO | 11 (48) |
| Corticosteroids | 11 (48) |
| Survival | 2/23 (9) |
| Death | 21/23 (91) |
| Died at age [d; median (range)] | 62 (3–150) |

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFO, high-frequency oxygenation; NO, nitric oxide; RDS, respiratory distress syndrome; SP-B, surfactant protein B.

Note: Data are given as *n* (%).

Diagnosis

Although prenatal diagnosis of SP-B deficiency is possible from 30 weeks' gestation onward using enzyme-linked immunosorbent assay (ELISA) in amniotic fluid⁴¹ and molecular diagnosis using DNA from either chorionic villi sampling (CVS) or amniotic fluid, it seems important that currently clinical genetic testing constitutes the diagnostic tool broadly available for clinicians⁴⁸. Analyses of amniotic fluid or, postnatally, bronchoalveolar lavage are limited to research laboratories and not available through clinical diagnostic laboratories.

Currently DNA analysis seems to constitute the most reliable diagnostic tool. Surfactant mutation analysis is well established in the United Kingdom⁴⁸; however, it remains difficult in many other countries. As stated by Turcu et al,⁴⁸ the rarity of the condition makes it difficult to develop a validated algorithm for genetic testing. International networking might be necessary.

Thin-section chest CT imaging may contribute important information when considering SFTPB deficiency.⁴⁹ Diffuse ground-glass opacity and markedly prominent interlobular septa suggesting alveolar proteinosis might be found.⁴⁹

Treatment

SP-B deficiency is a fatal disease with lung transplantation remaining the only theoretical treatment option. Maximum supportive therapy including sedation, muscle relaxants, inotropes, high-dose glucocorticoids, and intravenous gamma globulin is often needed. Mechanical ventilation, HFOV, inhaled nitric oxide, and even ECMO may be necessary to improve

oxygenation. However, any improvement of oxygenation in classic SP-B deficiency remains temporary with different effects according to phenotypic variations. HFOV combined with neuromuscular blockade often optimizes oxygenation for SP-B deficient infants, and therefore it might be considered while awaiting the diagnosis of SP-B deficiency and bridging to lung transplant.^{50,51} This treatment regimen decreases the synthesis, secretion, or accumulation of dysfunctional surfactant in the alveoli.⁹ Inhaled nitric oxide might be useful in infants who additionally developed pulmonary hypertension.⁵² Recurrent surfactant replacement therapy may or may not result in transient improvement of the respiratory condition, and even up to 80 doses of surfactant have been reported to be ineffective.⁸

Lung transplantation currently represents the only curative option available for SP-B deficient infants.^{9,50,53–55} Short-term outcomes for SP-B deficient infants who underwent lung transplant are comparable to those of infants who were transplanted due to other causes.^{9,56} However, data are based on several 16 infants. In addition, the 5-year survival rate for SP-B deficient infants who received a lung transplant constitutes 50% and equals the survival rate of infants who underwent lung transplant due to other causes.^{53,56} Short-term mortality is predominantly associated with infection whereas long-term mortality is predominantly due to bronchiolitis obliterans and infections, as well as lymphoproliferative malignancy.^{53,56} However, these results do not appear to be caused by SP-B deficiency but rather by lung transplant itself.^{53,56} Lung transplantation is associated with life-long immunosuppression therapy, lung denervation, and the possibility to develop SP-B antibodies.^{41,56,57} However, SP-B antibody production does not appear to be associated with poorer outcome.⁵⁶ Side effects and risks of life-long immunosuppressive therapy, as well as the need for close and consistent follow-up, the risks of complications, such as graft-versus-host disease, recurrent infections, and hospitalization all must be considered and discussed extensively with the parents.^{39,57,58}

Future Aspects

SP-B deficiency might be an ideal candidate for gene therapy because it constitutes a monogenic defect and is inherited recessively. So far, adenoviral vectors have shown potential to deliver SP-B complementary DNA (cDNA) to animal lungs.^{59,60} Gene therapy might be an approach for future curative therapies, but as compared with gene therapy in cystic fibrosis currently remains target to research.

Conclusion

Although knowledge on underlying genetic variations constantly increases and genetic testing as well as gene therapy is frequently progressing, SP-B deficiency still remains a very rare and usually fatal disorder primarily affecting term infants. Response to interventions such as exogenous surfactant administration and high-dose corticosteroids are only temporary and infants usually die within the first year of life. If an infant survives bridging to lung transplant—up to now 16 cases have been reported—this reflects the only curative

treatment option showing 5-year survival rates of 50%, which are comparable to infants who had undergone lung transplant due to other causes.

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