

## Surfactant Metabolism Dysfunction Type 3 (SMDP3)

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### Abstract

Surfactant (surface-active-agent) is a compound of phospholipids and proteins which are synthesized and secreted into the alveolus by type II epithelial cells, where it functions to decrease surface tension, maintaining alveolar expansion, to facilitate pulmonary compliance.

Surfactant Proteins (SP) A, B, C, D represent around 8% of total components, but has vital role in optimizing rapid adsorption and spreading of phospholipids. ATP-binding cassette sub-family A member 3, protein that encoded by *ABCA3* gene, which located in human chromosome 16p13.3, is synthesized in endoplasmic reticulum and migrated to lysosomal-derived organelles of alveolar type II cells, formally known as lamellar bodies. Once accumulate into the membrane, *ABCA3* can direct surfactant phospholipid into the lumen of lamellar bodies and create tight packed of surfactant lipids and proteins. Mutation of the ATP-binding cassette transporter Gene *ABCA3* cause failure in lamellar body synthesis and result in decreased production of surfactant, along with respiratory distress syndrome, and fatal respiratory failure.

**Keyword:** *ABCA3*; ATP-binding cassette transporter; Centrosome, Dallah Hospital; NICU

### Description

We report neonate with Surfactant metabolism dysfunction type 3, with critical acute respiratory distress syndrome, accompanied by respiratory failure in Riyadh, KSA. A 25-year-old gravid a two, Para one woman at 40 weeks gestation, with regular antenatal care, and normal prenatal screening, without chronic illness. The female infant is vigorous, and Apgar scores were 8 and 9 at 1 and 5 minutes of life respectively, baby transfer to nursery section in good condition with a birth weight of 3000 g. First degree relative consanguineous parents, they had first sibling born at 27 weeks gestation, who was Neonatal Intensive Care Unit (NICU) graduate, no family history of similar condition. At the age of two hours, the infant shifted to (NICU) secondary to respiratory distress. Respiratory rate was 70 per minute, oxygen saturation 86% on Bubble CPAP, temperature 36.5, tachypneic, chest recession and bilateral diminished air entry. No dimorphic features, heart sounds are audible in all auscultator areas, loud second heart sound is detected in pulmonary component, plus soft murmur, unremarkable neurological and abdominal examination. On admission, the infant connected to non-invasive ventilator support for 58 hours, then intubated and connected to mechanical ventilator due to desaturation beside increase oxygen requirement. During intubation, a fresh blood noticed in ET tube. Radiograph shows granular, hazy, ground-glass interstitial pacifications, Initial therapeutic dose of surfactant was given and followed by multi doses, which gave a little pit of improvement that allowed to keep patient out of invasive mechanical ventilator for 5 days. The infant has been kept between conventional and high frequency ventilators and death was announced by day 43 of life.

### Investigations

- Initial laboratory evaluation included a white blood cell count of  $17.98 \times 10^3/\mu\text{L}$ , with 21% neutrophils, 40% lymphocytes, 8% monocytes, hemoglobin 21 (g/dl), platelets 241, and CRP 21.98 (Tables 1 and 2) showed patient criterion, laboratory values and work up during hospital course (Figures 1-3).
- Genetic study: blood sample sent to Germany, cent gene labs showed: A homozygous pathogenic variant was identified in the *ABCA3* gene (Figures 4 and 5). The diagnosis of autosomal recessive surfactant metabolism dysfunction type 3 is confirmed.

Imaging	
Serial echocardiography	
ECHO	Moderate ASD2, small PDA and PPHN
CT chest	Bilateral diffuse ground glass attenuation throughout lungs field
Brain Ultrasound	Unremarkable
Abdomen & pelvis U. S	Unremarkable
Serials X-ray	Granular, hazy, ground-glass interstitial opacifications
Newborn screening	
Tandem Mass	Unremarkable
Gene study	
Centosome	Positive-homozygous pathogenic variant in <i>ABCA3</i> gene

Table 1: Work up during hospital course.



Figure 1: X-rays on admission, showed bilateral hazy, glandular pictures.

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Patient Criteria	
Gestational age	40
Mode of delivery	NSVD
Resuscitation at delivery	None
APGARS(1&5 min)	8&9
Gender	Female
Age at presentation	2 hours
Age of death	43 days
Laboratory values	
1 White blood cells(10 <sup>3</sup> /μL)	17.9
Neutrophils(%)	52.4
Lymphocytes(%)	31.2
Platelets (x 10 <sup>3</sup> /μL)	241
Culture	
Blood	Negative
Nasal swab	Negative
Urine	Negative
ETT aspirated secretion	Negative
Stool	Negative
Reparatory viral Panel(PCR)	Negative
CRP	21.9, 33.2, 52.5, 12.2, 7.5

Table 2: patient criteria, laboratory values and work up.



Figure 2: X-ray at day 3, showed increased, haziness, granularity and ground glass interstitial opacification.



Figure 3: X-ray, at day 7, more ground glass interstitial opacification.



Figure 4: X-ray, at day 15, dose not shows improvement, increased glandular pattern.



Figure 5: X-ray, at day 30, revealed severe ground glass interstitial opacification, almost white out lungs.

## Discussion

The genetic disorders of surfactant metabolism dysfunction are caused by mutations in genes encoding proteins which essential for both function and creation of pulmonary surfactant. It's rare disorders that may cause sporadic or familial lung disease, with clinical presentations ranging from neonatal respiratory failure to childhood or adult-onset interstitial lung disease. Beside the major surfactant proteins, additional proteins including *ABCA3* (member A3 of the ATP binding cassette family of proteins), the *TTF-1* (Thyroid Transcription Factor 1) are also important to produce functioning surfactant [1,2].

Surfactant Metabolism Dysfunction-3(SMDP3) is caused by homozygous or compound heterozygous mutation in the *ABCA3* gene and appears to be the most common cause of genetic surfactant dysfunction in humans [3-5]. Mutations which related to loss or functional defect of *ABCA3* protein are inherited in an autosomal recessive pattern [MIM #610921]. Two types of mutation are known, (Type1 mutation), which related to absent, decreased protein expression, or abnormal trafficking, while (Type 2 mutation) associated with diminished functional activity of *ABCA3* protein [6,7]. As supported by animal and human studies, severe neonatal form of the disease is thought to be result from functional surfactant defect [8,9]. In humans with *ABCA3* mutations, lack amounts of mature SP-C and altered processing of pro SP-B to SP-B have been observed [10].

*ABCA3* mutations vary in its presentation and severity, according to the part on the genotype, as shown in a series of 185 individuals with various *ABCA3* mutations. It is found that the most severe phenotype with (respiratory failure at birth, leading to death or lung transplantation by one year of age) was found in 100 percent of those with mutations predicted to preclude *ABCA3* expression on both alleles, as compared with 75 percent of those with genotypes of either null/other or mutations [11].

The carrier frequency in the population with *ABCA3* mutation has been estimated to be between 1 in 33 to 1 in 70 individuals, which predicting a disease incidence of between 1 in ~4400 to 1 in ~20,000 [12].

Surfactant dysfunction due to mutations in *ABCA3* has a more variable phenotype, depending in part on the genotype. The initial presentation with a severe RDS-picture in a full-term neonate. The resultant disease is progressive may leads to early death in some infants, while other infants may stabilize or improve. Patients with *ABCA3* mutations may also present later in infancy or childhood. Cough, tachypnea, hypoxemia, gastro esophageal reflux, and failure to thrive are frequent features [13].

## Conclusion

Full term babies with progressive respiratory distress, not responding to exogenous surfactant and ventilation support and highly consanguinity, increase vigilance and a high index of suspicion of congenital surfactant deficiency.

## Recommendation

We recommended parenteral carrier testing to confirm homozygosity of the variant in place of compound heterogeneity for large deletion.

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