New disease

Respiratory distress syndrome due to a novel homozygous *ABCA3* mutation in a term neonate

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Summary

The authors report, for the first time in the literature, a case of respiratory distress syndrome in a term baby due to homozygosity for a p.Trp308Arg/W308R substitution in the ATP-binding cassette transporter 3. The sequence was confirmed by genetic analysis of the baby and both parents. Management and long-term outcome of a patient carrying this novel genetic defect have not been reported in the literature before. Currently, lung transplant appears to be the only long-term survival option available, for which, our patient is being evaluated.

BACKGROUND

Surfactant deficiency respiratory distress syndrome (RDS) classically occurs in preterm babies due to gestational age-related deficient production of the surfactant. However, the condition can sometimes occur in term babies either secondary to consumption of surfactant (eg, meconium aspiration, pneumonia etc) or to congenital abnormalities of surfactant production.¹ Mutations in the genes encoding the surfactant proteins B and C (SP-B and SP-C) and the phospholipid transporter ATP-binding cassette transporter 3 (*ABCA3*) are well described among the genetic disorders disrupting normal surfactant metabolism. These disorders are also known as pulmonary surfactant metabolism dysfunctions or surfactant dysfunction disorders.² Recently, these genetic disorders have been recognised as the underlying cause of acute respiratory distress and respiratory failure in full-term neonates and interstitial lung disease (ILD) in older infants, children and adults with significant mortality and morbidity.²⁻³

ABCA3 is a large, integral membrane protein (figure 1) that is highly expressed in the type 2 alveolar cells and is localised primarily in the outer or limiting membrane of the lamellar bodies.⁴ *ABCA3* most likely functions to import surfactant phospholipids, such as phosphatidylcholine (PC) and phosphatidylglycerol, from the cytosol into the lamellar body.⁴⁻⁵ Hence, altered structure/deficient function of *ABCA3* can result in serious surfactant metabolism disorder. In this article, we are reporting a case of *ABCA3* dysfunction secondary to a homozygous loss-of-function mutation in the coding region of the *ABCA3* gene, which expressed itself as acute RDS in a full-term neonate with protracted course and significant morbidity. To our knowledge, among the known 150 distinct genetic mutations causing *ABCA3* dysfunction,² a homozygous loss-of-

function mutation in the coding region of the *ABCA3* gene has not been reported in the literature before. The challenges faced in the long-term management of these babies are also discussed in this report.

CASE PRESENTATION

A full-term baby girl was born by Caesarean section with a birth weight of 3.56 kg and an Apgar score of 9 and 10 at 1 and 5 min, respectively. Both parents are native of Qatar and first-degree maternal cousins. The mother is a 26-year-old primigravida with no risk factors for infection and with no significant family history. Maternal antenatal ultrasound (US) at 38 weeks had shown mild oligohydramnios with high indices on Doppler studies. The family history of both parents was unremarkable.

At the age of 3 h, the baby developed respiratory distress with tachypnoea and grunting, requiring admission to the neonatal intensive care unit. The baby initially needed only nasal continuous positive airway pressure (CPAP). However, due to worsening respiratory distress, she was ventilated and given two doses of surfactant, which resulted in a dramatic improvement. She was extubated to nasal canula within 48 h. Over the next week, she gradually developed worsening respiratory distress with increasing FiO_2 , requiring CPAP support. A chest x-ray on day 3 showed inhomogeneous ventilation of the lungs with areas of overinflation and reticular opacities (figure 2). A CT scan of the chest (figure 3) revealed a generalised reduced transparency with ground glass attenuation and accentuation of the interstitial spaces with interlobar septal thickening. A search for infectious and metabolic causes was negative. Congenital heart disease was excluded by a 2D Echo. She received multiple doses of surfactant with brief periods of improvement following each dose. Bronchoalveolar lavage

Figure 1 Lung surfactant and the lamellar body. The composition of lung surfactant is critical to lung function, and the subcellular lamellar body of the type II alveolar cell has a major role in maintaining the composition of surfactant. The distribution of ATP-binding cassette (ABC) transporter A3 (ABCA3) is shown in red. It is possible that ABCA3 targets surfactant-containing vesicles to the lamellar bodies. The lamellar body is formed through the fusion of several multivesicular bodies, and its lipid bilayers are converted to tubular myelin as they are turned out into the alveolar space. Surfactant protein A, secreted primarily by a constitutive pathway that does not involve the lamellar body, is required for the formation of tubular myelin. Surfactant aggregate, such as tubular myelin, is the precursor of surfactant at the air-water interface (inset). Cationic transmembrane proteins (surfactant protein B or surfactant protein C or both (not depicted in the monolayer-multilayer film)) together with anionic phospholipids (phosphatidylglycerol or phosphatidylinositol or both (green)) facilitate the entry of dipalmitoyl phosphatidylcholines (blue) into the monolayer at the interface, maintaining a low surface tension. During tidal breathing, tubular myelin surfactant is converted to smaller aggregates that are taken up by type II cells and alveolar macrophages. Arrows depict the direction of surfactant flux.⁸

(BAL) did not show any signs of inflammation or infection. Due to the progressive nature of the condition and the consanguinity of the parents, a congenital surfactant abnormality was suspected.

The parents declined a lung biopsy to exclude structural abnormalities of the lungs. In order to rule out an inherited disorder of the pulmonary surfactant system, a sequence analysis of the *SFTPB*, *SFTPC*, *CSF2RA* and *ABCA3* genes was performed, which revealed that the patient was a homozygous carrier of the loss-of-function mutation p.Trp308Arg (c.922T>C) encoded by exon 9 of the *ABCA3* gene. Both parents were confirmed to be heterozygous carriers of this mutation.

In addition to the established treatment of chronic respiratory failure and following confirmation of the diagnosis of surfactant deficiency due to an *ABCA3* mutation, she was started experimentally on oral hydroxychloroquine (10 mg/kg) for 4 months. However, we got the impression that this treatment did not significantly improve her respiratory status and it was therefore stopped. She remained dependent on nasal CPAP with brief periods of mechanical ventilatory support in between. Later, she became ventilator-dependent due to worsening chronic lung disease (figure 4). A short course of dexamethasone for 10 days failed to assist her extubation. Her liver function tests, serum electrolytes, ECG and echocardiogram were normal. During the last 8 months, she had two episodes of sepsis

(coagulase-negative *Staphylococcus* and *Enterobacter cloacae*). She also had recurrent episodes of ventilator-associated pneumonia (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Stenotrophomonas maltophilia*). The baby is now 13 months old, 9 kg in weight and on full enteral feeds via a nasogastric tube. She remains ventilator-dependent via tracheotomy and is currently undergoing assessment for a lung transplant.

INVESTIGATIONS

- ▶ BAL
- ▶ Genetic analysis of baby and both parents.

DIFFERENTIAL DIAGNOSIS

- ▶ Surfactant protein B deficiency
- ▶ Surfactant protein C deficiency.

TREATMENT

Lung transplant is the ultimate treatment available. Our patient is currently undergoing fitness tests for lung transplant in a centre in the USA.

OUTCOME AND FOLLOW-UP

Our patient has severe chronic lung disease and is ventilator-dependent via tracheotomy. Her follow-up after a possible lung transplant is awaited.

Figure 2 Chest radiograph showing respiratory distress syndrome (third day of life).

Figure 3 CT scan on day 16, showing generalised reduced transparency with interstitial accentuation.

Figure 4 Chest radiograph at 6 months of age.

DISCUSSION

Pulmonary surfactant is a complex mixture of lipids and proteins that is essential for normal lung function. Surfactant lowers the surface tension at the air-liquid interface, thereby preventing end-expiratory atelectasis. It is stored in lamellar bodies within alveolar type II cells and secreted into the alveoli by exocytosis. The production of pulmonary surfactant is developmentally regulated; hence surfactant deficiency RDS is a typical disorder of preterm babies. Rarely, surfactant deficiency disorder occurs in full-term newborn babies either due to a genetic deficient/defective production or secondary to consumption (eg, meconium aspiration, pneumonia, pulmonary haemorrhage etc). Surfactant proteins B (SP-B) and C (SP-C) are well-documented genetic disorders.⁶ Fatal surfactant deficiency RDS has also been reported in full-term infants in whom a deficiency of SP-B was excluded.⁷ The occurrence of familial cases suggests that additional genetic mechanisms are involved.⁷ Among these are mutations in the *ABCA3* gene, which have been shown to result in surfactant metabolism dysfunction (OMIM no. 610921).⁸ *ABCA3* disorders lead to abnormally formed lamellar bodies within type II pneumocytes, abnormal surfactant phospholipid composition and impaired processing of SP-B and SP-C precursors. The clinical presentation of *ABCA3* deficiency is very wide. It may present as acute neonatal RDS with a protracted course and significant morbidity as in our case. The disorder also presents as chronic ILD, manifesting at variable ages during childhood.⁹ This broad clinical presentation of *ABCA3* deficiency is probably due to its variable patterns of genetic mutation. Most described cases

are compound heterozygous. Anandarajan *et al*¹⁰ published a case report with two different mutations in the *ABCA3* gene in a term neonate, one inherited from each parent with no congenital deficiency of SP-B and SP-C. This baby had a very difficult intensive care course and required a trial of multiple modes of ventilation including high-frequency oscillatory ventilation and high-frequency jet ventilation in addition to 3 weeks of extracorporeal membrane oxygenation. She remained ventilator-dependent till she had a lung transplant at 20 months of age and was discharged home self-ventilating at 23 months of age. Poterjoy *et al*¹¹ recently reported another case of severe surfactant deficiency in a term female neonate due to an *SFTPC* mutation with no abnormalities in SP-B and *ABCA3*. This baby responded well to ventilator therapy but remained ventilator-dependent. She died on day 25 after parental consent for elective withdrawal of intensive care. In our case, the genetic abnormality was limited to a homozygous loss-of-function mutation in the coding region of the *ABCA3* gene without any additional abnormalities in *SFTPB*, *SFTPC* and *CSF2RA* genes. The homozygosity in our patient has most probably resulted in very severe clinical disease, with a protracted course and life long dependence on respiratory support. To our knowledge, this homozygous mutation has not been described in the literature before.

ABCA3 is a large gene located on chromosome 16 (16p13.3) and contains 30 coding exons.² More than 150 distinct mutations have been identified in the *ABCA3* gene,² making this the largest class of mutations that cause abnormalities in surfactant metabolism. The mutations are distributed throughout its length and consist of missense,

nonsense, frame shift and splice site mutations as well as insertions and deletions. The precise carrier rate of ABCA3 deficiency is unknown but may be more common than originally believed.^{10 12} Most described cases are compound heterozygous resulting in variable expression at various ages. In our case, both parents were heterozygous carriers of the ABCA3 p.Trp308Arg substitution. Hence, the inheritance was homozygous in our case. Homozygosity is known for an early and severe phenotypic presentation with a high incidence of mortality and morbidity. The protracted morbid course of our patient also confirms homozygous inheritance. Both parents of our patient are of Arabian inheritance with a consanguineous marriage. The rate of consanguinity is 40–70%¹³ among the Arabian countries in general and 54% in Qatar.¹³ Hence, the incidence of complex and unusual genetic disorders, including a high incidence of reproductive loss, is not a surprise in the Arab population.^{13 14}

Although the molecular genetic techniques are fundamental to the diagnosis of inherited metabolic disorders of surfactant deficiency, the histopathologic evaluation of lung tissue can be a valuable adjunct. Sentinel findings of a surfactant metabolic disorder include diffuse alveolar type II cell hyperplasia, alveolar septal thickening and alveolar proteinosis. Examination of the lamellar body morphology with electron microscopy can also provide an insight: disorganised lamellar bodies suggest SP-B deficiency while dense lamellar bodies or those with eccentric dense inclusions suggest ABCA3 deficiency.¹⁵ Unfortunately, in our case, the parents declined lung biopsy. Hence, we could not get valuable information on the histopathologic changes associated with this novel genetic mutation that could possibly have added to the future diagnosis and management of this order.

At the present time, there is no known specific treatment for infants with ABCA3 mutations.¹⁶ Babies with a milder disease have survived well beyond infancy with symptomatic treatment of their chronic respiratory disease. Some cases have been treated empirically with non-specific anti-inflammatory agents used in the management of ILD, including corticosteroids and hydroxychloroquine.¹⁷ Our patient was treated with steroids and a 6-month course of hydroxychloroquine with no clinical benefit. Although hydroxychloroquine has been used successfully in the treatment of a case of SP-C deficiency,¹⁸ which is attributed to its inhibition of intracellular processing of SP-C precursors, the efficacy of these agents in patients with lung disease due to ABCA3 mutations remains unknown. With improved diagnostic techniques and increasing number of diagnosed cases of ABCA3 deficiency, randomised clinical trials are urgently needed to establish the therapeutic role of hydroxychloroquine and other similar agents. Currently, the only possible curative treatment available is lung transplantation, without which most babies will not survive beyond 3–6 months of life.^{10 16} However, lung transplant is not a very easy option due to scarcity of available compatible donors as well as the technical and economic constraints and limited post-transplant life span (50% 5-year survival).¹⁵ The survivors also suffer from long-term morbidity due to bronchiolitis obliterans and lymphoproliferative malignancies. The post-transplant outcomes

of the inherited surfactant deficiency disorders are similar, suggesting that the outcomes are the consequences of transplantation rather than the underlying disease.¹⁹ While waiting for the lung transplant, the patients with severe lung disease pass through a protracted course of recurrent systemic and pulmonary infections, nutritional loss and significant social and psychological morbidity. Therefore, treatment options short of lung transplant must be explored.

The quality of survival of babies with chronic ventilator dependency is a critical factor in the family's decision-making on the long-term management. The degree and duration of illness in the pretransplantation period contributes significantly to the risk of adverse neurodevelopmental outcomes, especially in young infants. Nearly all ventilated infants suffer from oral-motor feeding difficulties that require long-term (1–2 years) nasogastric or gastrostomy feeding. Most infants have gross motor delays that improve in the first 2 years. Patients must also adhere to an extensive immunosuppressive regimen, regular monitoring of blood levels of immunosuppressive drugs, physical, occupational and speech therapy, and feeding interventions.¹⁵ These significant short and long-term challenges have prompted approximately half the families of affected children to decline lung transplantation and choose compassionate care for their infants. Due to parental preference, our patient has now been on the lung transplant waiting list. For almost 9 months she went through many difficult episodes of sepsis. She is currently being evaluated in the USA for suitability of lung transplant.

Learning points

- ▶ ABCA3 transporter deficiency is a genetic disorder that is being increasingly recognised as a cause of surfactant deficiency RDS in term babies and older children.
- ▶ The management of severe cases is limited to long-term intensive care support and empiric therapies.
- ▶ Prospective controlled studies using patients and animal models are urgently required to elucidate the pathophysiology of this condition and discover novel therapeutic interventions.

Competing interests None.

Patient consent Obtained.

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Parappil H, Al Baridi A, ur Rahman S, Kitchi MH, Ruef P, Griese M, Lohse P, Aslanidis C, Schmitz G, Koch L, Poeschl J. Respiratory distress syndrome due to a novel homozygous *ABCA3* mutation in a term neonate. *BMJ Case Reports* 2011;10.1136/bcr.10.2010.3427, date of publication

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