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Case Report

The First Saudi Case Report of Infrequent Mutation in ABCA-3 Gene

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Abstract

Respiratory distress symptoms manifest immediately after birth is common and can be due to abnormal respiratory function during transition from fetal to neonatal life. However persistent symptoms can be related to respiratory or non-respiratory causes. One of the comments causes of admission to Neonatal Intensive Care Unit (NICU) is respiratory distress syndrome (RDS) which can be either due to surfactant deficiency or defect in surfactant synthesis.

We are reporting a rare case of a non-dysmorphic Saudi neonate delivered by emergency lower segment cesarean section to a consanguineous parent with no living children, who lost their previous baby in early neonatal period with undiagnosed hypoxemic respiratory failure. Our baby presented immediately after birth with significant respiratory distress and progressive respiratory failure, chest x-ray and chest computed tomography scan (CT) were suggestive of diffuse interstitial lung disease. Patient received multiple doses of surfactant and maximum supportive therapy but unfortunately died at age of 38 days. Later, the result of Tri Whole Exome Sequence (WES) showed homozygous missense mutation c.4658T>C (p.Leu1553Pro) in ABCA3 gene which gives a pulmonary surfactant metabolism dysfunction which is pathogenic mutation, first to be described in Saudi population and reported before by others.

We aim from reporting this case: First, to suspect congenital defect in surfactant metabolism in any neonate with progressive respiratory distress/failure not responsive to any standard managements. Second, to call for collaboration between tertiary and other hospitals to facilitate the genetic diagnosis. And third, to encourage different societies' members with high authorities in the kingdom to establish a Saudi Childhood interstitial lung diseases (ChILDs)/Surfactant Mutations' Registry for initiation of a pediatric lung transplant program till genetic engineering therapy for such mutation sees the light, as every single life is valuable.

Keywords: *ABCA-3 mutation; Surfactant Protein Deficiency; Neonate; Pediatric; Respiratory Disease; Lung Developmental Disorders; Interstitial Lung Disease of Childhood; Genetic Disorders of Surfactant Dysfunction; Surfactant Metabolism Dysfunction; Inherited Pulmonary Disease; Pulmonary Surfactant; Surfactant Deficiency; Respiratory Distress Syndrome; Arab; Saudi Arabia; Al Qatif*

Abbreviations

ABCA3: ATP-Binding Cassette, Sub-Family A, Member 3; SP-B and SP-C: Surfactant Proteins B and C; ChILD: Childhood Interstitial Lung Disease; TTF-1: Thyroid Transcription Factor 1; NKX2.1: NK2 Homeobox 1; CT: Computed Tomography; RDS: Respiratory Distress Syndrome; CT: Computed Tomography; FiO_2: Fraction of Inspired O_2; NICU: Neonatal Intensive Care Unit; iNO: Inhaled Nitric Oxide; HFOV: High Frequency Oscillatory Ventilation; PGD: Preimplantation Genetic Testing; MAP: Mean Airway Pressure; WES: Whole Exome Sequence; AAV: Adeno-Associated Virus

Introduction

Respiratory distress symptoms manifest immediately after birth is common and can be due to abnormal respiratory function during transition from fetal to neonatal life. However persistent symptoms can be related to respiratory or non-respiratory causes [1]. One of the comments causes of admission to Neonatal Intensive Care Unit (NICU) is respiratory distress syndrome (RDS). RDS can occurs due to surfactant deficiency which is seen almost exclusively in premature infants or can occur due to congenital surfactant deficiency caused by mutations in various genes playing an important role in surfactant biosynthesis [2]. Pulmonary surfactant is a complex mixture of lipids, primarily dipalmitoyl phosphatidylcholine, surfactant proteins (SP-A, SP-B, SP-C, and SP-D), and the protein adenosine triphosphate-binding cassette subfamily A member 3 (ABCA3), produced by type II pneumocytes. Pulmonary surfactant is essential for lowering surface tension at the air–liquid interface to prevent end-expiratory alveolar collapse. Lamellar bodies are dense multilayer secretory organelles found in pneumocytes II which is responsible for final assembly of surfactant component prior to its secretion. ABCA3 is localized to the limiting membrane of lamellar bodies, selectively facilitates the transfer of lipids to lamellar bodies and protein maturation of surfactant. More than 150 recessive mutations of the ABCA3 gene have been reported in newborn babies which result in defective transport mechanism leading to incorrect composition and structure of surfactant.

Though rare, autosomal recessive mutations of ABCA3 gene are considered the most common inherited surfactant dysfunction. Its neonatal onset form manifests soon after birth as a severe RDS or respiratory failure and almost all these newborn infants die early within the first few months of life as no specific therapy exist and lung transplant is the only option that can extend the survival [3-6]. Few cases with ABCA3 mutation have been reported in Saudi Arabia [7-9].

We report a neonate who required resuscitation at birth due to perinatal depression and respiratory failure, genetic testing revealed homozygous missense mutation c.4658T>C (p. Leu1553Pro) in ABCA3 gene which gives a pulmonary surfactant metabolism dysfunction that is pathogenic mutation, first to be described in Saudi population and reported before by others.

Materials and Methods

Our case report and literature review from 2007-2022 through national library of medicine (PubMed https://pubmed.ncbi.nlm.nih.gov), a national center for biotechnology information, and from google scholar.

Consent

Written consent was taken from the parents for approval of case reporting and publishing.

Case Presentation

A Saudi baby boy was born at 39 weeks of gestation, to a 33-year-old healthy mother who was gravida 3 para 1+1. The baby was delivered by emergency lower cesarean section due variable deceleration in CTG with birth weight 2500 grams. Antenatal history was unsuggestive of maternal infection. The parents are first cousins with no living children. They have a previous daughter died shortly after birth with hypoxemic respiratory failure and severe pulmonary hypertension. The mother had history of one abortion at the second trimester. The baby born limp, bradycardic with poor respiratory efforts, required resuscitation including intubation, Apgar score was 3 and 7 at the 1st and 5th minutes respectively and transferred to NICU.

Initial examination there showed non dysmorphic neonate with significant respiratory distress and hypoxia with no difference between pre and post ductal saturation. Initial blood gas showed hypoxemic hypercapnic respiratory failure. The patient required sedation and adjustment of mechanical ventilation.

Hyperoxia test was done and showed response to oxygen with wide alveolar- arterial (A-a) gradient which is going with V/Q mismatch causes of hypoxemia.

Chest X ray showed Diffuse interstitial pattern (Figure 1). Initial and later serial echocardiography were normal. Initial basic laboratory workup was normal with negative blood culture.

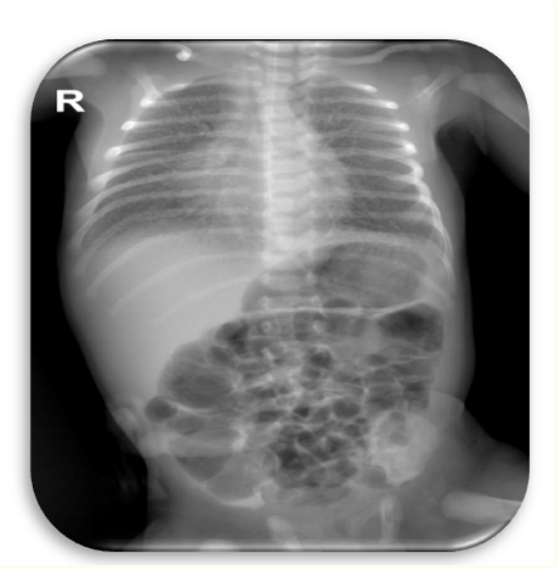

Figure 1: *CXR showed diffuse interstitial pattern.*

Childhood Interstitial Lung Disease (ChILD), alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV), surfactant production defect: (SFTPB, SFTPC, ABCA 3, NKX2.1) were all in the top of our differential diagnosis.

Due to progressive respiratory distress and high oxygen requirement patient was given a trial of surfactant at age of 15 hours but no improvement. At age of 36 hours, patient was shifted to high-frequency oscillatory ventilation due to high oxygenation index. Patient remained on mechanical ventilation with no improvement. Daily chest x ray done and showed a picture of ground glass opacity with air bronchogram apparently by day 10 of life (Figure 2).

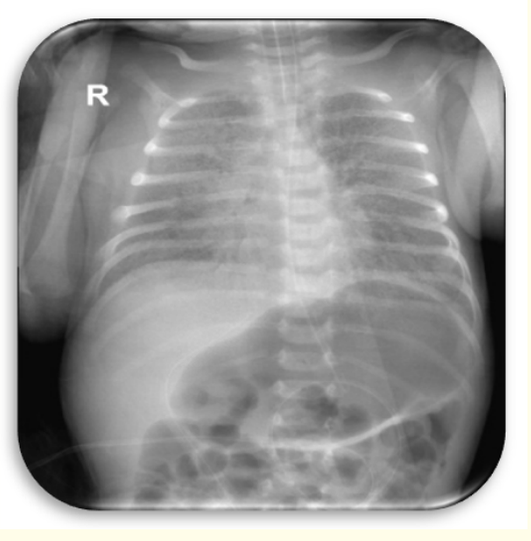

Figure 2: *CXR showed ground glass opacities and air bronchogram.*

Chest computed tomography (CT) scan showed diffuse bilateral ground glass opacities, bilateral diffuse dilated bronchi and bronchiole with interlobular septal thickening (Figure 3).

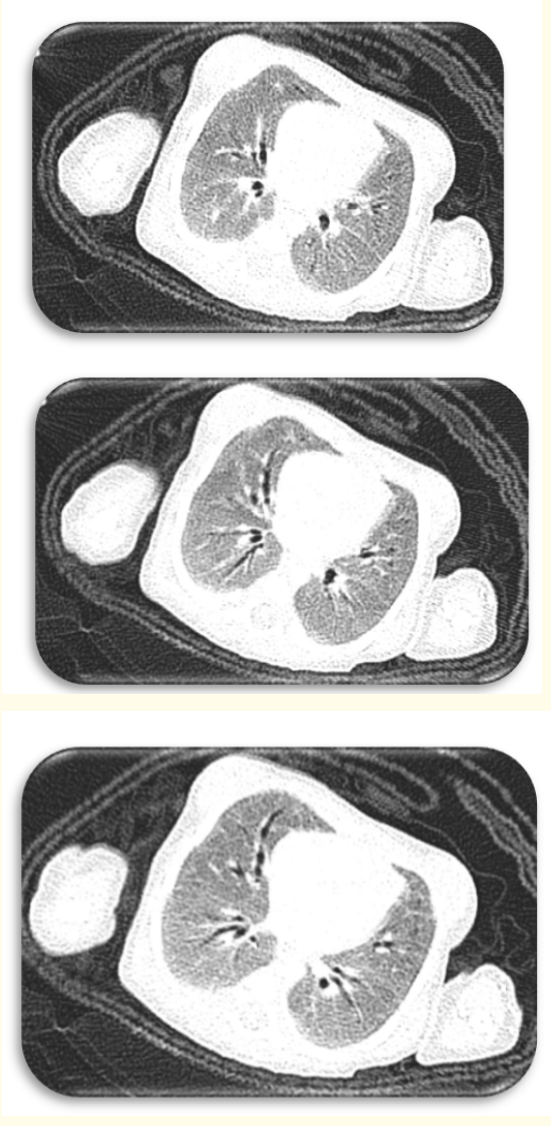

Figure 3: *Chest CT showed diffuse bilateral ground glass opacities, bilateral diffuse dilated bronchi and bronchiole, and interlobular septal thickening.*

Subsequent surfactant was given for a total of 5 doses with no clinical or radiological improvement. Lung biopsy is not feasible in our hospital. Considering the severe clinical course of our patient with radiological evidence suggestive of previously mentioned differential diagnosis, and death of his sister with similar clinical picture, whole exome sequence test was sent.

The baby remained in the same critical condition, on mechanical ventilation with maximum oxygen requirement and supportive therapy. His course was complicated by multiple episodes of sepsis and unfortunately died at age of 38 days.

The result of Trio Whole Exome Sequencing (WES) came after death, which showed pathogenic homozygous missense mutation c.4658T>C (p. Leu1553Pro) in exon 30 of ABCA3 gene, and parents are heterozygous carriers which confirm the diagnosis. Genetic counseling was provided to the parents and the mother was referred for Preimplantation Genetic Testing (PGD).

Results and Discussion

ABCA3 transports phospholipids that are critical for surfactant function into lamellar bodies. Defective transport of one or more components would be expected to lead to ineffective assembly of the structure and abnormal surfactant. Alternatively, ABCA3 could transport lipids that are deleterious to the function of surfactant out of lamellar bodies [10]. As the mode of inheritance of surfactant deficiency related to ABCA-3 mutation is an autosomal recessive, the prevalence of this condition increase in culture with high consanguineous marriage. The reported rate of consanguineous marriage in eastern province of Saudi Arabia namely Dammam city is (52%), First-cousin marriages were the commonest (39.3%) of all mattings [11]. No prevalence estimation is available in our Qatif city.

The incidence of this genetic disorder is not known, and only a few cases have been described to date. High index of suspicion as well as advanced investigations facilities such as genetic testing or lung biopsy and histopathology findings suggestive of the disease are needed to confirm the diagnosis. we speculate that many cases were missed because lacking the facility for proper diagnosis among different regions in Saudi Arabia.

Wambach., *et al*. suggested that the carrier rate of ABCA3 mutations could be as high as 1 in 30 individuals of European descent and 1 in 70 individuals of African descent, which projects a disease incidence ranging from 1:4,000 to 1:17,000 individuals. This relatively high incidence but low frequency of reported cases could imply that individuals with milder disease are unrecognized and underdiagnosed [12].

In this case report, we describe the first Saudi full-term neonate with infrequent variant in ABCA3 gene who presented with progressive and fatal respiratory failure . Clinical features were consistent with fatal surfactant deficiency. Chest X-ray and computed tomography scan findings involving all lung fields, in addition to no response to surfactant replacement therapy, may point to surfactant metabolism dysfunction.

Trio WES done and showed homozygous missense variants c.4658T>C (p.Leu1553Pro) in exon 30 of ABCA3 gene. Parents are obligates carriers. It's classified according to American College of Medical Genetics and Genomics (ACMG) as pathogenic and it's the first to be described in Saudi Population and reported before by others [10].

Up until now, nine cases have been reported in Saudi Arabia are linked to ABCA3 gene. Of them, five cases were confirmed to have homozygous non-sense mutation. The remining four had missense mutation. Phenotype and genotype of Saudi reported cases with ABCA3 mutation are attached in table 1.

The presence of missense variants is expected to be associated with milder phenotype than that associated with biallelic null variants (nonsense, frameshift, deletions, and splice-site) due to preservation of some residual protein function. For reviewed cases, the age of presentation and the survival rate is almost the same. Therefore, no obvious genotype to phenotype correlation. Keeping in mind, the sample of reviewed Saudi cases is small which could be either due to the under diagnosis of the disease or due to limitation of genetic testing. Therefore, to have a solid correlation between the genotype and phenotype, larger sample size is needed.

Multiple therapies have been mentioned in the literatures including surfactant, steroids and diuretics but all failed to slow the progression of the disease. Lung transplantation has been suggested in patients with milder mutations, as well as in those who have survived to childhood or adulthood. Nevertheless, children affected by mutations often die within 3 months after birth [13,14]. We didn't give any potential treatment other than trials of surfactants to our patient as we got the diagnosis by genetic testing later.

At these moments, gene therapy is a promising option to treat monogenic lung diseases. Developing gene therapies for genetic disorders of surfactant dysfunction which are targeting the alveolar type 2 epithelial cells including viral vector design and tropism for

Table 1: *Phenotype and genotype of Saudi reported cases with ABCA3 mutation.*

Case Number	Sex	Age of onset and initial presentation	Genetic testing	Age of death
1*	Male	Neonatal respiratory distress syndrome	Homozygous missense c.4658T>C (p.Leu1553Pro) in exon 30 of ABCA3 gene	6 weeks
2 [7]	Male	Neonatal respiratory distress syndrome	Homozygous missense c.4648T>G (p.Leu1553Pro) in exon 30 of ABCA3 gene	1 month
3 [7]	Male	Neonatal respiratory distress syndrome		2 months
4 [7]	Male	Neonatal respiratory distress syndrome		4 months
5 [7]	Female	Neonatal respiratory distress syndrome	Homozygous missense c.4444 C>T(p. Arg 1482Trp) in exon 29 of ABCA3 gene	2 months
6 [7]	Male	Neonatal respiratory distress syndrome	Homozygous nonsense c.4545C>G (p.Tyr1515*) in exon 29 of ABCA3 gene	2 months
7 [9]	Male	Neonatal respiratory distress syndrome		5 weeks
8 [8]	Female	Neonatal respiratory distress syndrome	Homozygous nonsense c.4545delC (p.Tyr1515*) in exon 29 of the ABCA3 gene.	Reached age of 2 years and 6 months, then lost follow up
9 [8]	Female	Mild respiratory distress symptoms after birth requiring supportive oxygen only		Underwent lung transplant at age of 1 year and 6 months at united state, no available data after that
10 [8]	Female	Neonatal respiratory distress syndrome		6 months

**Our case.*

target cell types as explored by adeno-associated virus (AAV), lentiviral, and adenoviral (Ad)-based vectors as delivery vehicles. Both gene addition and gene editing strategies are compared to best design treatments for lung diseases resulting from pathogenic variants in the SFTPB, SFTPC, and ABCA3 genes [15,16].

Conclusion

Genetic disorders of surfactant metabolism are underdiagnosed in our society due to limitation of genetic testing. We are reporting a term neonate who presented with severe lethal respiratory failure soon after birth who was found to have a pathogenic ABCA-3 mutation which confirm the diagnosis.

We aim from reporting this case: First, to suspect congenital defect in surfactant metabolism in any neonate with progressive respiratory distress/failure not responsive to any standard managements. Second, to call for collaboration between tertiary and other hospitals to facilitate the genetic diagnosis. And third, to encourage different societies' members with high authorities in the kingdom to establish a Saudi Childhood interstitial lung diseases (ChILDs)/Surfactant Mutations' Registry for initiation of a pediatric lung transplant program till genetic engineering therapy for such mutation sees the light, as every single life is valuable.

Conflict of Interest

No conflict of interest exists.

Funding Support

None.

Ethical Approval

The Institutional Review Board (IRB) approved this study (IRB Log Number: 18-389). Written informed consent was obtained from the patient's father for the publication of this case report and all accompanying images.

Contribution of Authors

All the authors were involved in the writing and editing of the manuscript. All the authors read and approved the final manuscript.

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