A New *ABCA3* Gene Mutation Presenting as Early Neonatal Surfactant Deficiency

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Abstract

Mutations of the ATP-binding cassette transporter A3 gene (*ABCA3*) causing the dysfunction of surfactant proteins are a well-established cause of interstitial lung disease. The clinical presentation is variable ranging from neonatal early death to mild forms of interstitial lung disease in the adult. We present the case of a newborn with early neonatal respiratory distress. The clinical and radiologic findings were compatible with interstitial lung disease. The disease progressed toward severe respiratory insufficiency and the patient died at the age of 3 years. A variant not yet described in the literature was found in the *ABCA3* gene (c.4442C>T), in apparent homozygosity. Parental genetic studies revealed that only the father was a carrier for this variant. The quantitative study of the *ABCA3* gene in our patient revealed a deletion affecting exon 32 and possibly 29. This report describes the phenotype of a new *ABCA3* variant causing surfactant deficiency while also highlighting the importance of considering gene deletions in case of unconfirmed homozygosity.

Keywords: ATP Binding Cassette Transporter, Subfamily A/deficiency; ATP Binding Cassette Transporter, Subfamily A/genetics; Lung Diseases, Interstitial/etiology; Lung Diseases, Interstitial/diagnosis; Lung Diseases, Interstitial/mortality; Newborn; Pulmonary Surfactant-Associated Proteins/genetics; Respiratory Distress Syndrome, Newborn/etiology

Introduction

Interstitial lung disease can have a wide range of etiologies. Inborn errors of surfactant metabolism, which consist of genetic mutations resulting in the altered or null activity of the surfactant proteins, can cause respiratory disease in the neonatal and pediatric populations and ultimately result in interstitial lung disease. The deficiency of surfactant protein B was the first genetic cause identified, resulting in surfactant dysfunction. Mutations in the other genes encoding surfactant proteins as surfactant protein B (*SP-B*) and ATP-binding cassette transporter A3 (*ABCA3*) were identified later.[1]

Concerning *ABCA3* dysfunction (MIM 601615) - which encodes protein adenosine triphosphate (ATP) binding cassette, subfamily A, member 3, a surfactant protein - it was firstly described in 2004 in a group of newborns with fatal neonatal respiratory distress. Although the disease was initially associated with this phenotype, subsequent studies have shown that a great number of older children suffering from interstitial lung disease of unknown etiology ended up having *ABCA3* mutations.[3,4] These findings suggest that there is a great variety of phenotypes regarding *ABCA3* mutations and that the prevalence of *ABCA3* mutation causing interstitial lung disease is underestimated. To date, there are more than 200 *ABCA3* mutations reported including small deletions.[5]

The protein encoded by the *ABCA3* gene is located on human chromosome 16 that contains 33 exons.[6] The mutations described to date are distributed throughout the large *ABCA3* gene and present as nonsense, missense, and frameshift mutations as well as insertions or deletions. These mutations usually result in the diminished production of the protein, altered function of the protein, abnormal intracellular transport, or impaired ability to hydrolyze ATP or to transport phospholipids across membranes, and are expressed in an autosomal-recessive manner.[7,8]

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Case Report

Female patient, born at 39 weeks of gestation in Luanda. No relevant familial history and absence of paternal consanguinity. The patient had two older healthy brothers. The pregnancy and delivery were uneventful.

A few hours after birth, the patient developed respiratory distress syndrome with tachypnea, retractions, cough, cyanosis, and crackles at auscultation. Immediate oxygen supplementation was needed. Chest radiography revealed a bilateral diffuse interstitial pattern.

The patient needed hospitalization since birth due to oxygen dependence and at the age of 4 months was transferred to Lisbon, Portugal. At this point, an exhaustive etiologic investigation for the respiratory insufficiency was made. The echocardiogram revealed a structurally and functionally normal heart. The thoracic computed tomography angiography revealed bilateral ground-glass opacification, and zones of air trapping (Fig. 1) and excluded arterial-venous malformations.

Laboratory investigation revealed negative TORCH group serologies, normal cellular and humoral immunity, and a negative sweat test. Metabolic study and karyotype were normal.

Bronchofiberscopy, excluded tracheoesophageal fistula, and no significant gastroesophageal reflux was diagnosed. After excluding other possible etiologies, the diagnosis of interstitial lung disease seemed likely. The pulmonary biopsy showed areas of atelectasis, septal thickening, pneumocyte hyperplasia, and iron-laden macrophages (Fig. 2). These findings were suggestive of chronic pneumonitis of infancy. Due to its early onset, a genetic cause for surfactant dysfunction was sought. Deoxyribonucleic acid (DNA) analysis of *ABCA3*, surfactant protein B (*SFTPB*), and surfactant protein C (*SFTPC*) demonstrated an apparent homozygous variant in the *ABCA3* gene c.4442C>T. The parental study was also performed and showed that only the father was a carrier of this variant. Since *ABCA3* dysfunction is an autosomal recessive disorder, a quantitative study of *ABCA3* was performed in this patient to search for a possible deletion. The study revealed a heterozygous deletion c.(?_4910-1)_(4983+1_?)del in the gene *ABCA3*.

Regarding clinical evolution, the patient was discharged after the investigations but remained oxygen-dependent and with labored breathing. She needed noninvasive ventilation mainly during respiratory infections that were frequent and almost always requiring hospital admission. She also developed feeding difficulties and failure to thrive which was managed with hypercaloric feeding given through a nasal gastric tube. Despite this, the patient never developed pulmonary hypertension.

From the therapeutic point of view, she was managed with systemic and inhaled steroids, bronchodilators, hydroxychloroquine, aminophylline, and diuretics. The patient was also discussed among a multidisciplinary team regarding a pulmonary transplantation involving pneumology and cardiothoracic surgery with expertise on pulmonary transplantation. The young age and the low weight of the patient, in addition to poor nutrition status, were considered factors of a very poor prognosis in this case. Moreover, in the national centers, there is very limited experience regarding pulmonary transplantation in children this small.

The patient experienced progressive worsening of the degree of hypoxemia and respiratory distress and died at the age of 3 in the context of a severe respiratory infection.

Quantitative study method

Real-time quantitative polymerase chain reaction (qPCR) amplification (Rotor-Gene Q, QIAGEN, Germany)

Figure 1. Image of thoracic computed tomography scan showing bilateral ground glass opacification as well as zones of air trapping.

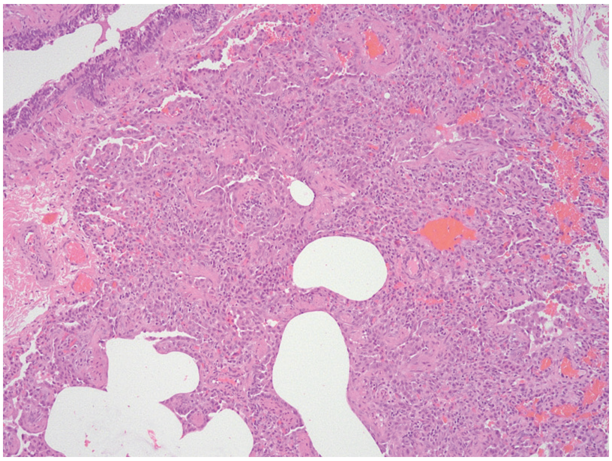

Figure 2. Image of pulmonary biopsy showing areas of atelectasis, septal thickening, and pneumocyte hyperplasia.

was performed using specific primers for the target areas of the studied gene. These regions were selected according to the alterations described in the human gene mutation database) database when applicable.[5] The samples were identified as deleted, duplicated, or with no alteration, according to the established limits.

Discussion

Surfactant protein dysfunction is a very heterogeneous group of diseases. Concerning *ABCA3* dysfunction, its relevance in interstitial lung disease is relatively recent since its association with severe neonatal respiratory distress and interstitial lung disease was established recently.

Several reports showed that *ABCA3* gene mutations were not only associated with neonatal respiratory disease and interstitial lung disease but also with milder forms of interstitial lung disease in older patients. Ever since then, several different mutations in this gene have been described.

The *ABCA3* gene is a large gene and different types of mutations can occur throughout the entire gene. This helps in explaining the great phenotype variability described so far.

Although several variants continue to be identified, their clinical significance is not always clear. A *ABCA3* mutation in a premature infant with chronic respiratory insufficiency was described and the authors demonstrated, through functional analysis, that it severely compromised the *ABCA3* protein function.[11] Several other studies identified mutations in the *ABCA3* gene in term infants with respiratory failure.[4,12-17] These are autosomal recessive mutations, frequently identified in subjects with a positive family history.

It was shown that most *ABCA3* mutations were homozygous or compound heterozygous, but a small number of these patients had the *ABCA3* mutation in only one allele.[2] These patients could have a second mutation on the other allele that could be within introns, regulatory regions, or a deleted region.

In our patient, a genetically determined surfactant deficiency was suspected due to the clinical, radiologic, and histopathological findings. A homozygous missense variant was identified, and as far as we know, it is a variant that has not been described in the literature yet. A missense variant can be either a benign polymorphism or a deleterious mutation. As this variant was identified in a highly conserved residue of the gene, it is probably deleterious. In addition, the suggestive clinical presentation and the negative search for mutations in the other surfactant protein genes support this hypothesis.

The parental study revealed that only the father was a carrier of the variant. To search for a possible deletion in our patient, a quantitative study of the *ABCA3* gene was performed and that allowed us to confirm the presence of a deletion. This result supports the clinical diagnosis of a pulmonary surfactant metabolism dysfunction type 3 (MIM#610921), which is an autosomal recessive transmissible disease caused by mutations in the *ABCA3* gene. This result indicates that the apparent homozygous variant c.4442C>T (p.Ala1481Val) detected in the next-generation sequencing (NGS) (CGC 699462) panel is actually a compound heterozygosity. The variant detected is a heterozygous deletion that affects at least exon 32 and most probably also affects exon 29, which is where the variant was detected. This deletion is not described in the literature or in polymorphism databases as yet. A large deletion on the *ABCA3* gene was previously reported,[18] but it was homozygous. With the available data, this variant should be considered as a highly probable pathogenic one.

As for parental genetic counseling, the parents were informed of the 25% chance of recurrence. Prenatal screening and genetic diagnosis pre-implantation were offered in a future pregnancy.

WHAT THIS CASE REPORT ADDS

- *ABCA3* mutations have a large spectrum of clinical presentations.
- A new *ABCA3* gene mutation and its phenotype are described.
- The genetic testing in early interstitial lung disease presentation is important.
- Considering gene deletions in case of unconfirmed homozygosity is important.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Uma Nova Mutação do Gene *ABCA3* com Apresentação de Deficiência de Surfactante Neonatal Precoce

Resumo:
Mutações no gene que codifica transportadores de cassetes de ligação de ATP A3 (*ABCA3*) são uma das causas de disfunção das proteínas do surfactante pulmonar e consequentemente de doença intersticial pulmonar. A apresentação clínica varia desde doença respiratória neonatal grave a doença intersticial pulmonar ligeira em jovens adultos. Este caso clínico retrata uma criança com insuficiência respiratória neonatal cujos achados clínicos e radiológicos eram compatíveis com doença intersticial pulmonar. A doença progrediu para insuficiência respiratória grave culminando no óbito aos 3 anos de idade. O estudo genético revelou uma variante no gene *ABCA3* (c.4442C>T) ainda não descrita na literatura, em aparente homozigotia. O estudo genético parental revelou que apenas o pai era portador desta variante. O estudo quantitativo do gene *ABCA3* foi realizado na nossa paciente revelando uma deleção afetando o exão 32 e possivelmente o 29. Este caso clínico reporta o fenótipo de uma nova variante do gene *ABCA3* e realça a importância de considerar deleções genéticas em casos de homozigotia não confirmada.

Palavras-Chave: Doenças Pulmonares Intersticiais/etiologia; Doenças Pulmonares Intersticiais/diagnóstico; Doenças Pulmonares Intersticiais/mortalidade; Proteínas Associadas a Surfactantes Pulmonares/genética; Recém-Nascido; Síndrome do Desconforto Respiratório do Recém-Nascido/etiologia; Subfamília A de Transportador de Cassetes de Ligação de ATP/deficiência; Subfamília A de Transportador de Cassetes de Ligação de ATP/genética