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CASE REPORT

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Neonatal meconium aspiration syndrome associated with ABCA3 gene mutation and mycoplasma infection: a case report

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Abstract

Preterm infants are at high risk of developing respiratory distress syndrome (RDS). Mutations in the genes encoding for surfactant proteins B and C or the ATP-binding cassette transporter A3 (*ABCA3*) are rare but known to be associated with severe RDS and interstitial lung diseases. The exact prevalence of these mutations in the general population is difficult to determine, as they are usually studied in connection with clinical symptoms. Most cases are not captured due to variability in expression or diagnosis. It is estimated that they affect a small percentage of the population, with mutations in *ABCA3* most commonly identified in association with severe lung diseases in newborns. Even heterozygous *ABCA3*-mutations can increase the risk and severity of RDS in neonates. The expression of these proteins is developmentally regulated, increases with gestational age, and is crucial for the function of pulmonary surfactant at birth. Additional lung stressors, such as meconium aspiration syndrome or pulmonary infections, can lead to a complex clinical picture associated with severe courses. This case report describes an extremely preterm female infant with suspected meconium aspiration syndrome, severe RDS, Mycoplasma pneumoniae infection, and a heterozygous *ABCA3*-mutation. The report discusses the clinical presentation, diagnostic evaluation, and therapeutic interventions, emphasizing the complexities associated with multiple pulmonary conditions in the context of extreme prematurity. At the limits of viability, therapeutic options for severe respiratory insufficiency are limited compared to older children. The developmental neurological prognosis following prolonged relative hypoxia is a crucial factor to consider in discussions about changing treatment goals. Particularly in severe cases, pulmonary infections and genetic changes in surfactant metabolism must be considered in newborns with RDS.

Keywords Preterm infant, Respiratory distress syndrome, *ABCA3*-mutation, Mycoplasma pneumoniae, Case report

Introduction

Preterm infants are at high risk of developing respiratory distress syndrome (RDS). Mutations in the genes encoding surfactant proteins B and C or the ATP-binding cassette transporter A3 (*ABCA3*) are rare but known to be associated with severe RDS and interstitial lung diseases. The expression of these proteins is developmentally regulated, increases with gestational age, and is crucial for the function of pulmonary surfactant at birth. Heterozygous *ABCA3*-mutations can also increase the risk of RDS in neonates. Additional lung stressors, such as meconium aspiration syndrome or pulmonary infections, can lead to

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a complex clinical picture in newborns, often associated with severe courses.

Patient information

A 32-year-old primigravida with diet-controlled gestational diabetes presented at 27 + 4 weeks of gestation after preterm premature rupture of membranes (pPROM) from an external hospital.

Clinical findings and timeline

- *27 + 4 weeks of gestation*: Admission with pPROM; antenatal corticosteroids for fetal lung maturity and prophylactic antibiotics were administered.
- *27 + 6 weeks of gestation*: Development of greenish amniotic fluid led to the decision for a secondary cesarean section. Foetal heart rate was normal.
- *Birth*: The infant was bradycardic (< 60 bpm) despite adequate ventilation (100% FiO2); immediately transferred to the neonatal intensive care unit (NICU).
- *Diagnostic Assessment*: In the NICU, the infant weighed 1340 g (87th percentile), body length was 37 cm, and head circumference was 27 cm. APGAR scores were 5/9/9. Umbilical cord pH was 7,39. A chest X-ray showed a fine-granular pattern in all lung fields, together with the greenish amniotic fluid, it was raising suspicion of meconium aspiration syndrome. An echocardiogram revealed signs of pulmonary hypertension. Whole-exome sequencing identified a heterozygous missense mutation c.920 C > T (p.Ala307Val) in exon 9 of the *ABCA3*-gene. Tracheal secretions (PCR, DNA) tested positive for Mycoplasma pneumoniae.

Therapeutic intervention

The infant received

- *Day 1*: Cardiopulmonary resuscitation, endotracheal intubation, 480 mg of surfactant, and antibiotic therapy with ampicillin and gentamicin for seven days.
- *Following Days*: Inhaled nitric oxide for pulmonary hypertension and bronchoscopy showing patent airways. An additional 240 mg of Curosurf was administered.
- *Weeks 1–6*: Sodium chloride inhalation, azithromycin therapy, and diuretic therapy with hydrochlorothiazide.
- *Days 2–10*: Hydrocortisone was initiated on day two and switched to dexamethasone on day ten, tapered, and discontinued after 26 days.

Follow-up and outcome

The patient was successfully extubated after 22 days, subsequently on continuous positive airway pressure (CPAP) with a maximum FiO2 of 61%. Due to persistent oxygen requirements, diuretic therapy continued for two weeks, and inhalations with salbutamol and fluticasone via AeroChamber were administered. CPAP/highflow therapy was discontinued 55 days after extubation, and supplemental oxygen was stopped after 77 days.

Discussion

Pulmonary adaptation is a challenge for all newborns. Extremely preterm infants often have difficulties producing surfactant, leading to RDS. Suspected meconium aspiration exacerbates the precarious pulmonary situation. An additional mutation in the *SFTPB*, *SFTPC*, or *ABCA3* gene further impairs surfactant production, increasing the burden on the system. Respiratory infections are the most common cause of morbidity and mortality in newborns. Mycoplasma pneumoniae is frequently associated with respiratory tract infections in children over five years old. The infection rate with Mycoplasma pneumoniae in neonatology is 8.2% and should also be considered a potential source of infection. The distribution of primary infection varies. Mycoplasma pneumoniae infection increases with age. Newborns aged 1–7 days are 3%, 8–14 days 12.4%, 15–21 days 31%, and 22–28 days 52% affected. Symptoms are usually mild and generally do not require oxygen or ventilation therapy. When three conditions (RDS, heterozygous *ABCA3*-mutation, and Mycoplasma infection) combine, symptom exacerbation can be suspected and can lead to severe respiratory insufficiency. As the patient's condition worsened progressively, oxygen saturation levels between 70 and 80% were achieved despite oxygen supplementation up to 100% uncertainty about the neurological outcome of the patient (persistent hypoxemia), it led to multiple conversations with the patient´s parents about changing the treatment. The therapy was continued, but not escalated.

In our case, the patient, in whom we suspected interstitial lung disease, responded successfully to dexamethasone therapy and additional azithromycin therapy. Dexamethasone therapy in newborns is a much-discussed medical issue. On the one hand, positive effects like higher rates of successful extubation and ductus arteriosus closure such as lower rates of severe retinopathy are described in literature. On the other hand, the therapy can be associated with gastrointestinal bleeding, intestinal perforations, hyperglycemia, hypertension, hypertrophic cardiomyopathy, or growth retardation and

cognitive delay. Our patient did not experience any of the above-mentioned complications.

The timing of Mycoplasma infection in our patient is uncertain. The swab was positive on day 23, while maternal immunoglobulins were IgG and IgM positive when searching for the infection source (two days after the patient's positive result), indicating mother-to-infant transmission. The patient did not develop IgM.

In summary, the administration of surfactant twice, early antibiotic therapy against atypical pneumonia pathogens, and switching to dexamethasone led to successful treatment. Genetic analysis and regular tracheal secretion assessments confirmed our therapeutic approach.

Patient perspective

The parents were actively involved in discussions about treatment goals and were supportive of the therapeutic interventions pursued.

Informed consent

Written informed consent for publication of clinical details and/or clinical images was obtained from the patient's parents.

Conclusion

This patient presented a combination of pulmonary diseases that exacerbated the respiratory symptoms of RDS in the context of extreme prematurity. At the limits of viability, therapeutic options for severe respiratory insufficiency are limited compared to older children. The developmental neurological prognosis following prolonged relative hypoxia is a crucial factor to consider in discussions about changing treatment goals. Particularly in severe cases, pulmonary infections and genetic changes in surfactant metabolism must be considered in newborns with RDS.

Introduction

It is known that preterm infants are at high risk of developing respiratory distress syndrome (RDS). Mutations in the genes encoding for surfactant proteins B and C or the ATP-binding cassette transporter A3 (ABCA3) are rare but known to be associated with severe RDS and interstitial lung diseases [1–3]. The exact prevalence of these mutations in the general population is difficult to determine, as they are usually studied in connection with clinical symptoms. Most cases are not captured due to variability in expression or diagnosis. It is estimated that they affect a small percentage of the population, with mutations in *ABCA3* most commonly identified in association with severe lung diseases in newborns. Even heterozygous *ABCA3*-mutations can increase the risk and severity of RDS in neonates [4]. The expression of these proteins is developmentally regulated, increases with gestational age, and is crucial for the function of pulmonary surfactant at birth. Additional lung stressors, such as meconium aspiration syndrome or pulmonary infections, can lead to a complex clinical picture associated with severe courses [5].

Patient

We report on an extremely preterm female infant with suspected meconium aspiration syndrome, severe RDS, Mycoplasma pneumoniae infection and a heterozygous *ABCA3*-mutation.

Case report

A 32-year-old primigravida (with diet-controlled gestational diabetes) presented at 27+4 weeks of gestation after preterm premature rupture of membranes (pPROM) from an external hospital. Upon admission, she received antenatal corticosteroids (betamethasone 12 mg i.m.) for induction of fetal lung maturation, atosiban for tocolysis (6,75 mg as a bolus and then 75 mg i.v. for three days), and prophylactic antibiotic therapy (azithromycin 1 g single shot and ampicillin 2 g every 8 hours). In addition, prenatal magnesium neuroprotection (magnesiumsulfat 3x400 mg) was administered. Routine maternal serologies were negative and the antibody screening test was negative. The rubella antibody test was positive. The maternal blood type was O positive. A swab for Group B streptococcus (GBS) was taken from an intrapartum vaginal swab and was sterile. At 27+6 weeks of gestation, the mother expelled greenish amniotic fluid, leading the indication for a secondary cesarean section. Foetal heart rate was normal. She delivered a female infant. The infant was bradycardic (<60 bpm) despite adequate ventilation (100% FiO2) and was immediately transferred to the neonatal intensive care unit (NICU). The infant weighed 1340 g (87th percentile), length was 37 cm and head circumference was 27 cm. The APGAR scores were 5/9/9 due to a heart rate below 100 beats/min, respiratory distress, pink trunk coloration with blue extremities, and decreased tone and reflexes. Cardiopulmonary resuscitation (three cycles) was performed in the first minute of life. Umbilical cord pH was 7,39. The heart rate subsequently rose above 120 beats/min. After 10 minutes, clinical signs of RDS with an oxygen requirement of 60% were observed. The infant was intubated and received 480 mg of surfactant (Curosurf®).

Antibiotic therapy with ampicillin and gentamicin was administered intravenously for seven days. Blood cultures remained sterile. To verify tube placement and investigate oxygenation issues, a chest X-ray was performed, showing a fine-granular pattern in all lung fields, raising suspicion of meconium aspiration syndrome. An

echocardiogram revealed signs of pulmonary hypertension, prompting inhaled nitric oxide therapy. Upon deterioration in oxygenation, echocardiographic follow-up after nitric oxide therapy cessation, showed no evidence of pulmonary hypertension. A bronchoscopy revealed patent airways without increased mucus. Another 240 mg of surfactant was administered.

Suspecting interstitial lung disease, sodium chloride was inhaled and azithromycin was administered orally initially for three days, followed by a therapy every two days. This regimen continued for six weeks. Additionally, the patient received a diuretic therapy with hydrochlorothiazide (2 mg/kg) for three weeks. The patient's oxygenation improved at times, but repeated ventilation issues due to increased secretion occurred. Tracheal secretions (PCR, DNA) tested positive for Mycoplasma pneumoniae on the twenty-third day considered the cause of severe RDS.

The patient's condition worsened progressively. Oxygen saturation levels between 70 and 80% were achieved despite oxygen supplementation up to 100%. Persistent hypoxemia and the uncertainty about the neurological outcome of the patient, led to multiple conversations with the patient´s parents about changing the treatment. The therapy was continued, but not escalated.

Persistent ventilation problems and clinical suspicion of surfactant deficiency syndrome led to urgent genetic testing in the newborn. Therefore whole-exome sequencing (Twist Comprehensive Exome + Mitochondrial Panel (Twist Bioscience)) on NextSeq2000 (lllumina) as 2x150 bp „paired end reads" was performed on genomic DNA. Analysis of the target genes *TBX4, BMPR2, SMAD9, ENG, ALK1, ABCA3, SFTPB, SFTPC, SFTPA1, SFTPA2, CSF2RA, CSF2RB, FLNA, FOXF1, NKX2-1, TTF-1, GATA2, SLC7A7, MARS, NPC2, NPB, FOXP1, TMEM173, CFTR* in the SeqNext module (JSI, Germany) and genes related to the Genomics England PanelApp (https://panelapp.genomicsengland.co.uk/panels/) primary ciliary disorders (Version 1.42), surfactant deficiency (Version 1.11) and PanelApp Australia (https://panelapp.agha.umccr.org/panels/) Ciliary Dyskinesia (Version 1.38) identified the heterozygous missense mutation c.920C>T (p.Ala307Val) in exon 9 of the *ABCA3*-gene (Submission number: RCV004732503.1), after using the filtering programs varSEAK (JSI, Germany) and VarSeq (Golden Helix, USA). The silico tool REVEL predicts this genetic mutation to be pathogenic (0,834). This mutation is found only once in 1614242 alleles in gnomAD v4.1.0. The mutation was previously reported in a preterm (27 weeks) with lung disease and respiratory distress in homozygous state, as well as in a 2 year old child with *ABCA3*-deficiency in homozygous state [6, 7]. There was still a strong clinical suspicion of an association with severe lung disease in the heterozygote state. According to literature, patients with *ABCA3*-mutations respond well to systemic corticosteroid therapy with dexamethasone. In our patient, hydrocortisone was initiated on the second day of life (before receiving genetic testing) and changed to dexamethasone on the tenth day. The dexamethasone therapy (0,5 mg/kg) was tapered (to 0,3 mg/kg) and discontinued after 26 days. Afterwards hydrochlorothiazide was again initiated (2 mg/kg) for two weeks. After 22 days, the patient was successfully extubated. Subsequently, she was on CPAP with a maximum FiO2 of 61%. Due to persistent oxygen requirements, diuretic therapy with hydrochlorothiazide and spironolactone was continued for two weeks. Additionally, inhalations with salbutamol and fluticasone via Aerochamber were administered. CPAP/highflow therapy was discontinued 55 days after extubation. Supplemental oxygen was stopped after 77 days.

Discussion

Pulmonary adaptation is a challenge for all newborns. Extremely preterm infants often have difficulties producing surfactant, leading to RDS. Suspected meconium aspiration exacerbates the precarious pulmonary situation [5]. An additional mutation in the *SFTPB*,*SFTPC*, or *ABCA3* gene further impairs surfactant production, increasing the burden on the system [1, 8]. Respiratory infections are the most common cause of morbidity and mortality in newborns. Mycoplasma pneumoniae is frequently associated with respiratory tract infections in children over five years age. The infection rate with Mycoplasma pneumoniae in neonatology is about 8% and should be considered a potential source of infection [9]. The distribution of primary infection varies. Mycoplasma pneumoniae infection increases with age. Newborns aged 1–7 days are 3%, 8–14 days 12.4%, 15–21 days 31%, and 22–28 days 52% affected. Symptoms are usually mild and generally do not require oxygen or ventilation therapy [10]. When three conditions (RDS, heterozygous *ABCA3* mutation, and Mycoplasma infection) combine, symptom exacerbation can be expected. In our case the timing of Mycoplasma infection is uncertain. The respiratory swab was positive on day 23. Furthermore, the patient did not develop IgM after the positive respiratory swap. Maternal immunoglobulins were IgG and IgM positive when searching for the infection source (two days after the patient's positive result), indicating mother-to-infant transmission. In our case, the patient, in whom we suspected interstitial lung disease, responded successfully to dexamethasone and additional azithromycin therapy.

Dexamethasone is a much-discussed medical issue in newborns. On the one hand, positive effects like higher rates of successful extubation and ductus arteriosus

closure such as lower rates of severe retinopathy are described in the literature. On the other hand, the therapy can be associated with gastrointestinal bleeding, intestinal perforations, hyperglycemia, hypertension, hypertrophic cardiomyopathy, or growth retardation and cognitive delay [11, 12]. Due to the lack of improvement after initiation of hydrocortisone therapy, we decided to change the therapy to dexamethasone. Our patient did not experience any of the above-mentioned complications.

In summary, the administration of surfactant twice, early antibiotic therapy against atypical pneumonia pathogens, and switching to dexamethasone led to successful outcome. Genetic analysis and regular tracheal secretion assessments confirmed our therapeutic approach.

Conclusion

Our patient presented a combination of pulmonary diseases that exacerbated the respiratory symptoms of RDS in the context of extreme prematurity. At the limits of viability, therapeutic options for severe respiratory insufficiency are limited compared to older children. The developmental neurological prognosis following prolonged relative hypoxia is a crucial factor to consider in discussions about changing treatment goals. Particularly in severe cases, pulmonary infections and genetic changes in surfactant metabolism must be considered in newborns with RDS.

Protein sequences

Protein sequences consist of ordered chains of amino acids, determined by the nucleotide sequence of the corresponding gene. In this case, the p.Ala307Val mutation alters the ABCA3 protein sequence by replacing alanine with valine at position 307. This substitution may disrupt protein function by altering its biochemical properties, such as hydrophobicity or structural stability.

DNA and RNA sequences

DNA and RNA sequences represent the linear arrangements of nucleotides (adenine, thymine/uracil, cytosine, guanine). The mutation c.920C>T in the ABCA3 gene indicates a single nucleotide substitution where a cytosine (C) is replaced by a thymine (T) at position 920. This results in a codon change, altering the encoded amino acid from alanine to valine at position 307 in the ABCA3 protein.

DNA and RNA sequencing data

DNA and RNA sequencing data provide comprehensive information about the nucleotide arrangement in the genome or transcriptome. This mutation, c.920C>T, would be identified through high-throughput sequencing methods like whole-exome sequencing (WES) or RNA sequencing (RNA-seq). Such data are crucial for pinpointing pathogenic variants linked to diseases, including those affecting surfactant metabolism.

Genetic polymorphisms

Genetic polymorphisms refer to variations in the DNA sequence that occur frequently in a population and are generally considered benign. However, the mutation c.920C>T in the ABCA3 gene is classified as a rare missense variant rather than a benign polymorphism. Its location within a functionally critical region of ABCA3 suggests its potential involvement in surfactant-related disorders.

Linked genotype and phenotype data

Genotype-phenotype correlation studies explore the relationship between genetic variants and observable traits or diseases. The c.920C>T mutation in ABCA3 has been linked to impaired surfactant production in the lungs, which can lead to neonatal respiratory distress syndrome or interstitial lung disease. These findings highlight the clinical significance of linking genetic changes to specific phenotypic outcomes.

Macromolecular structure

The three-dimensional structure of macromolecules, including proteins, determines their function. The p.Ala307Val mutation may affect the folding or stability of the ABCA3 protein, potentially disrupting its ATP-binding cassette transporter function, which is essential for surfactant lipid transport in alveolar cells. Structural studies using crystallography or computational modeling can provide insights into these changes.

Microarray data (MIAME-Compliant)

Microarray data are used to study gene expression patterns and must comply with MIAME (Minimum Information About a Microarray Experiment) standards to ensure reproducibility. Microarray analyses of ABCA3-related pathways could reveal how the c.920C>T mutation influences the expression of genes involved in surfactant metabolism, potentially exacerbating lung pathology.

Crystallographic data for small molecules

Crystallographic data detail the atomic structure of small molecules, enabling the design of targeted drugs. In the context of the p.Ala307Val mutation, structural studies of surfactant components or interacting molecules could aid in developing therapies that compensate for the impaired ABCA3 function.

Abbreviations

RDS	respiratory distress syndrome
ABCA3	ATP-binding cassette transporter A3
pPROM	preterm premature rupture of membranes
GBS	Group B streptococcus
NICU	Neonatal intensive care unit
CPAP	Continuous positive airway pressure

Supplementary Information

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Supplementary Material 1.

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Clinical trial number
Not applicable.

Authors' contributions
OS and EG wrote the primary version of the manuscript. All authors reviewed the manuscript. Detailled author contributions are mentioned in the manuscript under declarations before the references.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
According to the local guidelines in Austria for publication of a case report no ethic vote is needed. Written informed consent for publication of clinical details and/or clinical images was obtained from the patient's parents. The authors thank the parents of the patient for their consent to publish this report.

Consent for publication
Written informed consent for publication of clinical details and/or clinical images was obtained from the patient's parents.

Competing interests
The authors declare no competing interests.

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