Neonatal Respiratory Insufficiency Caused by an (Homozygous) *ABCA3*-Stop Mutation: a Systematic Evaluation of Therapeutic Options

Neonatale Ateminsuffizienz durch eine homozygote *ABCA3*-Stopp-Mutation: systematische Evaluation der Therapieoptionen

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- medical treatment
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Abstract

Background: Autosomal recessive *ABCA3* (ATP-binding cassette protein A3) gene mutations have been associated with neonatal respiratory distress and pediatric interstitial lung disease. The clinical course of the disease depends on the underlying mutations. Therefore, knowledge of course, symptoms and treatment of the disease is important.

Patient and Methods: A term newborn suffered from progressive respiratory insufficiency, which led to death at the age of 4.8 months. The girl developed interstitial lung disease. Infections as well as structural and functional disorders of the lung were systematically excluded. A homozygous c.4681C>T (Arg 1561 Stop) mutation of the *ABCA3* gene was identified. A literature review of the pathophysiology and treatment options of the disease was done. Therapeutic approaches with corticosteroids, macrolide, and hydroxychloroquine did not improve the clinical course.

Results: Therapeutic strategies for chronic interstitial lung disease have been used successfully in cases of a mild clinical course in juvenile patients with *ABCA3* gene mutation. In our patient with homozygous *ABCA3* gene mutation, they were not effective. Lung transplantation remains as a therapeutic option, but because of donor organ shortage and associated morbidity and mortality it is rarely feasible.

Conclusion: More experience in the treatment of newborns with *ABCA3* gene mutations is needed. Randomized, prospective evaluation of the different therapeutic approaches in a specific registry may improve prognosis and treatment of affected individuals.

Zusammenfassung

Hintergrund: Autosomal rezessiv vererbte *ABCA3* (ATP-binding cassette protein A3)-Mutationen sind mit schwerem neonatalem Lungenversagen und chronischer interstitieller Lungenerkrankung assoziiert. Der klinische Verlauf der Erkrankung ist stark von den zugrunde liegenden Mutationen abhängig. Aus diesem Grund sind Verlaufsbeschreibungen zu Symptomatik und Therapie wichtig.

Patientin und Methodik: Ein reifes Neugeborenes litt an einer progredienten respiratorischen Insuffizienz, die im Alter von 4,8 Monaten zum Tod führte. Gleichzeitig entwickelte sich eine interstitielle Lungenerkrankung. Infektionen, funktionelle Störungen und strukturelle Lungenerkrankungen wurden systematisch ausgeschlossen. Ursächlich lag eine homozygote c.4681C>T (Arg 1561 Stop)-Mutation des *ABCA3*-Gens vor. Eine ausführliche Literaturrecherche zur Pathophysiologie und Therapie der Erkrankung wurde durchgeführt. Therapieversuche mit Corticosteroiden, Makrolid und Hydroxychloroquin erbrachten keine relevante Verbesserung der klinischen Situation.

Ergebnisse: Die genannten Therapieansätze werden bereits bei Patienten mit *ABCA3*-Mutationen angewendet und sind bei milden klinischen Verläufen erfolgreich. Bei unserer Patientin mit homozygoter *ABCA3*-Stopp-Mutation hatten sie keinen Effekt. Die Therapieoption der Lungentransplantation wird im Säuglingsalter wegen Spenderorganmangels und assoziierter Morbidität und Mortalität nur selten realisiert. Nach ausführlicher Evaluation wurde diese Therapiemöglichkeit bei unserer Patientin verworfen.

Schlussfolgerung: Es besteht Notwendigkeit, mehr Erfahrungen in der Behandlung von Neugeborenen mit *ABCA3*-Mutationen zu sammeln. Therapieoptionen sollten in einem Patientenregister systematisch erfasst und möglichst randomisiert prospektiv evaluiert werden, um so Prognose und Betreuung der Patienten zu verbessern.

Introduction

The autosomal recessive ATP-binding cassette protein A3 (ABCA3) gene defect is one of the rare differential diagnoses of respiratory distress syndrome (RDS) in the newborn period. The gene defect results in disorders of surfactant metabolism. The clinical course of the disease is highly variable depending on the underlying mutations of the *ABCA3* gene. In the presence of 2 defective alleles, affected newborns suffer from severe RDS and die early in infancy [25]. However, there are also cases observed in patients with *ABCA3* gene mutations showing a mild course of the disease and revealing chronic interstitial lung disease [6, 18]. Frequently, in these patients the underlying mutation permits a residual function of the ABCA3 transporter. Over 180 "loss of function" *ABCA3* gene mutations of the gene, which is located on chromosome 16p13.3, have been identified in association with lethal RDS in newborns or with chronic respiratory insufficiency associated with progressive interstitial lung disease in later infancy and childhood [18, 29]. The frequency of diseases due to the *ABCA3* gene defect in the population is unknown.

Pulmonary surfactant is a phospholipid-protein complex which is synthesized and secreted from type II alveolar cells [27]. ABCA3 is a 1704 amino acid transport protein. It is found mainly in the lungs, but also in many other tissues. It is proposed to be a phospholipid transporter into cells, which are involved in surfactant metabolism. ABCA3 is expressed at the luminal plasma membranes of type II alveolar cells, at the limiting membrane of multivesicular bodies and predominantly at the limiting membrane of lamellar bodies. The lamellar bodies of type II alveolar cells are responsible for the final assembly of the surfactant components prior to its secretion [8, 18]. The defective transport mechanism due to *ABCA3* gene mutation leads to incorrect composition and structure of the surfactant (for details see ○ **Fig. 1**). So far, no specific treatment strategies for patients with *ABCA3* gene mutations are available. Systematic studies have not been conducted. In the following case report we present the clinical course of a patient with fatal homozygous *ABCA3* gene mutation. In addition, we elucidate our differential diagnostic considerations and the successive application of therapeutic strategies.

Case report

We report the case of a full-term spontaneously born female newborn (40+3 gestational weeks, birth weight 3730 g, APGAR score 9/10/10). She was the third child of consanguineous Moroccan parents. The immediate postnatal adaptation was uncomplicated. The mother previously had had 2 abortions in early pregnancy. The 2 brothers of the patient do not have pulmonary disease. In the family history there were no neonatal deaths or severe pulmonary diseases in the newborn period.

Within 8 h of life the baby developed respiratory distress with cyanosis and was transferred to the NICU (neonatal intensive care unit). As infection was suspected, the child was treated immediately with ampicillin and gentamicin. The first X-ray showed no significant abnormalities. With increasing fraction of inspired oxygen (FiO_2) and dyspnea, the child was intubated on day 3 of life and was ventilated (synchronized intermittent mandatory ventilation (SIMV)). An X-ray at this time showed diffuse reticular pattern. Surfactant (100 mg/kg/dose Alveofact®, Lyomark Pharma) was administered on day 3 and 7 of life. FiO_2 and ventilation improved only little and for a short time period. With increasing mean airway pressure and increasing FiO_2 high frequency oscillation ventilation (HFO) was used from day 4 to 6, 8 to 21 and 24 to 50 of life. After the administration of dexamethasone (0.5 mg/kg/d) from day 8–10 of life only a short-term improvement of the respiration resulted. Because of pulmonary hypertension a therapy with inhaled nitric oxide (iNO) was initiated from day 7 to 21 of life. FiO_2 increased steadily and the chest X-ray showed an increasing reticular pattern. A therapy with hydroxychloroquine from day 16 to 32 of life (6–10 mg/kg/d in 2 doses) and prednisolone from day 26 to 32 of life (2 mg/kg/d) was given in order to treat an interstitial lung disease. In addition, diuretic treatment was given. To cope for recurrent hypoxic episodes a permanent sedation of the patient was implemented. After the diagnosis of a genetic *ABCA3* gene mutation, treatment with erythromycin from day 55–98 of life was initiated (10 mg/kg/dose every 6 h) and a second course of hydroxychloroquine was administered from day 98 to 135 of life. 2 pulse therapies (300 mg/m²BSA/d for 3 days) of methyl prednisolone were con-

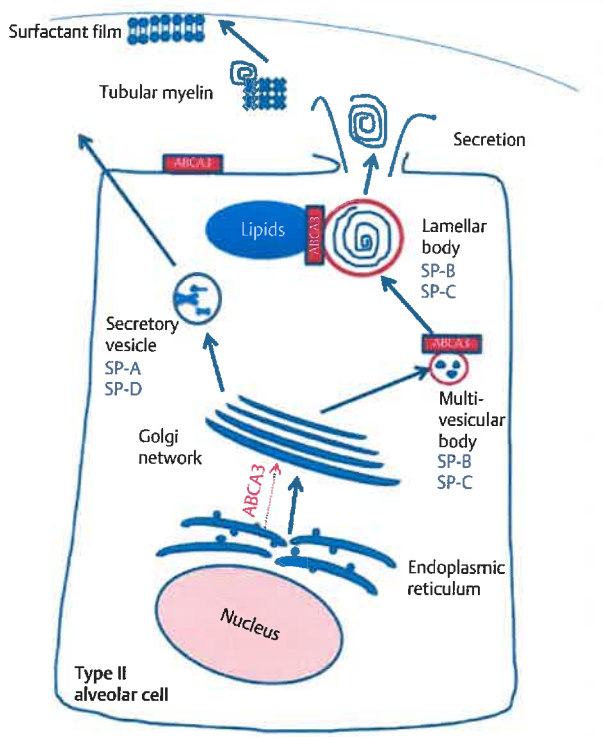

Fig. 1 Pulmonary surfactant metabolism. The genes encoding SP-A, pro-SP-B and pro-SP-C are transcribed in the nucleus of type II alveolar cells, translated into polypetides in the endoplasmic reticulum and processed in the golgi network. SP-B and SP-C are assembled into lamellar bodies along with surfactant phospholipids. Transport of the latter may be regulated by the ABCA3-transporter, predominantly located at the limiting membrane of these organelles. SP-A and SP-D are secreted via non-lamellar body secretory vesicles. Following exocytosis of lamellar bodies and secretory vesicles into the alveolar space ("Secretion"), lamellar bodies assemble into structures known as tubular myelin. Phospholipids from these structures move to form the surfactant film that lines the alveolar space [27]. *ABCA3* gene mutations are proposed to be classified into 2 categories: abnormal intracellular trafficking with abnormal intracellular localization of the protein (type I) and decreased ATP-hydrolysis activity of ABCA3 with normal intracellular trafficking (type II) [21, 22]. ABCA3 (ATP-binding cassette protein A3), SP-A (surfactant protein A), SP-B (surfactant protein B), SP-C (surfactant protein C), SP-D (surfactant protein D).

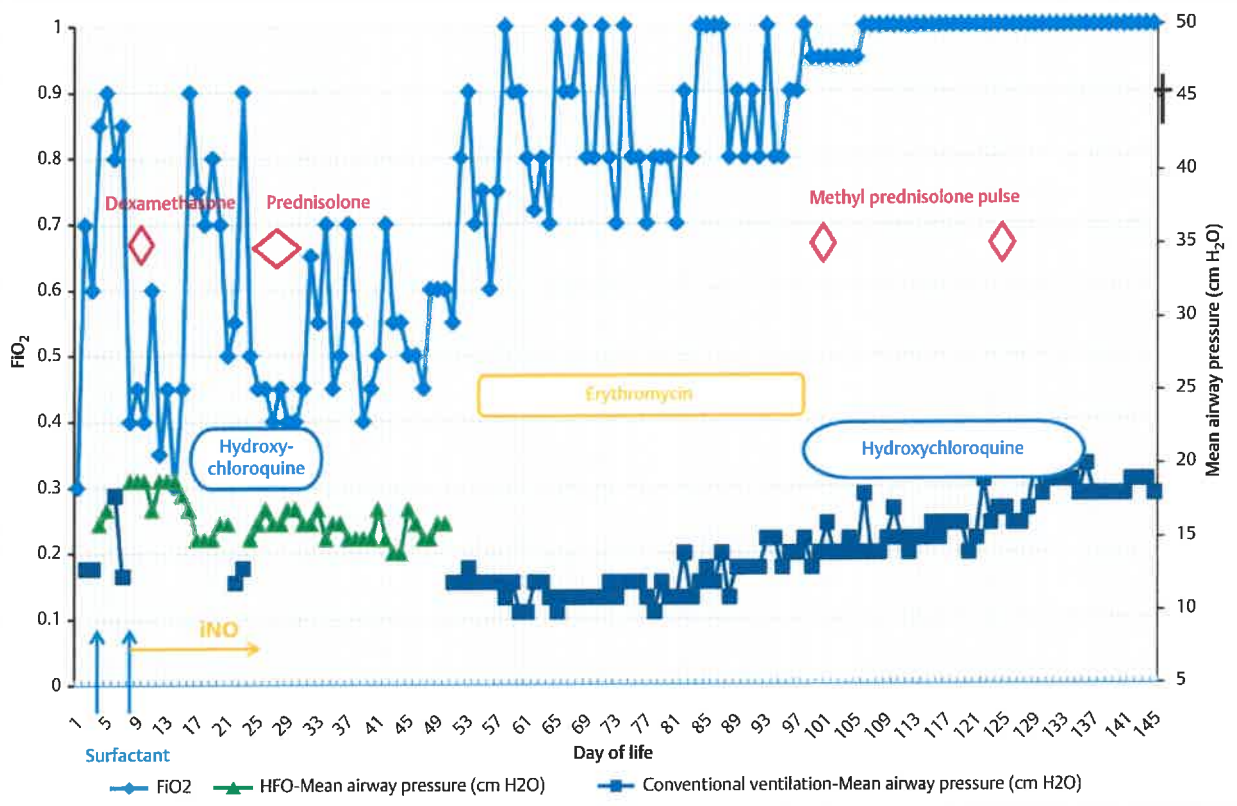

Fig. 2 Timing of therapy and ventilatory support.

ducted with an interval of one month. ○ **Fig. 2** summarizes the timing of therapy and ventilatory support. An improvement of respiration was not achieved.

On day 61 of life a Broviac-catheter was implanted and a tracheostomy was done on day 71 of life. Repeatedly, we recorded a rise of the patient's temperature with leukocytosis without an increase in C-reactive protein or Interleukin 6. A Picorna virus infection (detection by polymerase chain reaction (PCR) from laryngo-pharyngeal secretion) on day 94 of life again worsened the respiration. The patient suffered from frequent episodes of cyanosis and hypoxemia, after day 106 of life the FiO_2 was 1,0. The mean airway pressure gradually increased, reaching values up to 20 cm H_2O. The patient developed global respiratory insufficiency and died at the age of 145 days on our NICU. An autopsy was refused by the parents.

Differential diagnosis of respiratory failure

Numerous causes of respiratory failure in newborns were studied systematically (see ○ **Table 1a–d**). Infections, including bacterial, viral, atypical pathogens and fungi, functional disorders, and structural lung diseases were excluded. A lung biopsy was refused by the parents. A DNA analysis to clarify genetic surfactant metabolism disorder was carried out. Direct sequencing of the surfactant protein B gene (*SFTPB*), surfactant protein C gene (*SFTPC*) and *ABCA3* gene and the granulocyte-macrophage colony-stimulating factor (*GM-CSF*) receptor gene were performed. Anti-GM-CSF receptor antibodies were not detected in the serum. After sequencing of the coding part (30 exons) of the *ABCA3* gene, a homozygous c.4681C>T (Arg 1561 Stop) mutation was identified. The father was heterozygous for the c.4681C>T (Arg 1561 Stop) mutation of the *ABCA3* gene found in the child. The mother refused the examination of her blood.

Discussion

Our patient suffered from a severe form of an *ABCA3* gene mutation with rapidly progressive interstitial lung disease. The underlying mutation has already been described in the literature. That patient had died at the age of 3 months from respiratory insufficiency [4].

Pathophysiology and genetics

The present homozygous c.4681C>T Arg 1561 Stop mutation causes a termination of translation. It is likely that this leads to an incomplete and functionally inactive ABCA3 protein.

The mechanism which generates the heterogeneity and severity of the phenotype of pulmonary disease caused by *ABCA3* gene mutations is probably dependent on the underlying mutation [21]. In the literature there are numerous case reports of infants with *ABCA3* gene mutations who were seriously ill and died early in infancy [4–6,25]. On the other hand cases in which patients with *ABCA3* gene mutation show a mild course of the disease presenting as chronic interstitial lung disease are described [7,14,18]. Apparently there are mutations in the *ABCA3* gene which allow a residual function of the *ABCA3* transporter, so that the severity of the disease is reduced [21,29]. In severely affected children surfactant deficiency determines the clinical presentation [25]. The loss of key epithelial features may disturb the integrity of the alveolar epithelium causing intersti-

Table 1a Differential diagnosis of respiratory distress syndrome in newborns + / – transition to chronic interstitial lung disease. **Infection/pneumonia.**

Cause	Clinical signs	Diagnosis
Common pathogens (Bacteria)	*increased inflammatory markers, reduced general condition*	*clinical and laboratory evidence, cultures*
Rare pathogens e. g. Mycoplasma, Ureaplasma, Chlamydia, Legionella, Mycobacteria, Pneumocystis jirovecii, fungi	*increased inflammatory markers, reduced general condition*	*clinical and laboratory evidence, cultures, PCR, microscopy, detection of acid-fast bacilli*
Virus e.g. RSV, Influenza, Enterovirus	*increased inflammatory markers, reduced general condition*	*ELISA/PCR-testing in pharyngeal-/tracheal secretion and stool*
Intrauterine infections e.g. TORCH, HIV	*history, associated anomalies*	*serological and urine tests*

Table 1b Differential diagnosis of respiratory distress syndrome in newborns + / – transition to chronic interstitial lung disease. **Functional disorders.**

Cause	Clinical Signs	Diagnosis
Heart failure	*variable*	*echocardiography*
Maternal diabetes	*macrosomia, surfactant deficiency*	*history*
Cystic fibrosis	*respiratory failure, meconium ileus*	*immunoreactive trypsin, sweat test, mutation detection*
Ciliary dysfunction	*respiratory distress syndrome in the neonatal period, later otitis, rhinitis, chronic cough, sinusitis*	*brush border cytology with video microscopy*
Meconium aspiration	*dyspnea, oxygen demand*	*medical history, x-ray*
Niemann-Pick disease	*hepatosplenomegaly*	*elevated chitotriosidase, skin biopsy*

Table 1c Differential diagnosis of respiratory distress syndrome in newborns + / – transition to chronic interstitial lung disease. **Changes in lung structure.**

Cause	Clinical Signs	Diagnosis
Alveolocapillary dysplasia abnormal development of the capillaries to the alveoli [3]	*persistent pulmonary hypertension associated with urogenital or gastrointestinal malformations*	*lung biopsy*
Pulmonary interstitial glycogenosis maturation defect of interstitial cells containing glycogen [12]	*tachypnea, hypoxemia, response to corticosteroids*	*HR-CT, lung biopsy*
Neuroendocrine cell hyperplasia of infancy hyperplasia of neuroendocrine cells [13]	*tachypnea, intercostal retractions, hypoxemia, continuous clinical improvement*	*lung biopsy, detection of bombesin like peptide (immunohistochemistry) or HR-CT*
Congenital pulmonary lymphangiectasia extension of subpleural, interlobar, perivascular and peribronchial lymph vessels of the lungs [2]	*respiratory distress syndrome, tachypnea, cyanosis*	*MRI, lymphatic scintigraphy, pulmonary function tests, lung biopsy, bronchoscopy and analysis of pleural exudates*

Table 1d Differential diagnosis of respiratory distress syndrome in newborns + / – transition to chronic interstitial lung disease. **Disturbance of Surfactant metabolism/Alveolar proteinosis.**

Cause	Clinical Signs	Diagnosis
***SP-B* (Surfactant protein B) or *SP-C* (Surfactant protein C) gene mutation**	*respiratory failure in newborns (SP-B and SP-C) or chronic interstitial lung disease (SP-C)*	*mutation detection, bronchoalveolar lavage, determination of surfactant protein B or C, lung biopsy*
***GM-CSF* (Granulocyte macrophage-colony-stimulating factor) receptor gene mutation or anti-GM-CSF-antibody**	*respiratory failure (so far not been described in neonates)*	*mutation detection, antibody detection*
***ABCA3* (ATP-binding cassette protein A3) gene mutation**	*respiratory failure in newborns or chronic interstitial lung disease*	*mutation detection* ***x_1 in our patient homozygous c.4681C>T (Arg 1561 Stop) mutation***
***TTF1* (Thyroidal transcription factor-1) gene mutation**	*congenital hypothyroidism, chorea-like symptoms, RDS*	*mutation detection*

In our patient, either the typical symptoms of the diseases listed above were not present, or the conducted investigations provided inconspicuous results. Only the examination marked with x_1 revealed a positive result.

tial lung disease with fibrosis in children with *ABCA3* gene mutations and may be negatively triggered by additional factors such as virus infections [19]. Our patient was seriously ill directly after birth. Picorna virus infection, detected at day 94 of life, worsened the course of the disease and possibly increased lung fibrosis.

Matsumura et al. classified 2 types of *ABCA3* gene mutation. On the one hand, mutations that are associated with abnormal intracellular trafficking of ABCA3 (type I). On the other hand, mutations that are associated with normal intracellular trafficking, but with decreased ATP-hydrolysis activity of ABCA3 (type II). Patients with homozygous mutations of type I or type I/type II compound heterozygous *ABCA3* gene mutations died of the disease in the neonatal period. *ABCA3* type I gene mutations on one allele does not result in a fatal surfactant deficiency. Homozygous type II gene mutations were not identified by the authors [21,22]. ○ **Fig. 1** illustrates the proposed mechanism of *ABCA3* gene mutations.

The homozygous c.4681C>T (Arg 1561 Stop) mutation of our patient probably can be classified as type I mutation. The studies by Matsumura et al. show that other stop codon mutations (i. e., W1142X and Ins1518fs) are associated with an incorrect localization of ABCA3 and therefore can be assigned to type I mutations [22].

Interestingly, there is an E292V mutation variant of the *ABCA3* gene, this "missense" mutation results in an only partially impaired lipid transport function [21]. E292V was overrepresented in newborns with RDS suggesting that E292V increased genetic risk for RDS (about 4%). Affected newborns are described to recover from their lung disease [17]. Likewise, the mutation has been found in children with mild disease and chronic interstitial lung disease [7].

In comparison to other disorders of surfactant metabolism, the *ABCA3* gene mutation appears to occur frequently. *ABCA3* gene mutations were identified in 10 out of 47 children with diffuse lung disease (including 6 pre-term infants of gestational age < 36 weeks) with either severe RDS or a family history compatible with autosomal recessive inheritance. 9 of them (90%) had a severe respiratory distress syndrome, 5 patients died of respiratory failure in the first year (heterozygous and compound heterozygous mutations), 5 progressed to a chronic interstitial lung disease (homozygous, heterozygous and compound heterozygous mutations) [16].

The clinical and radiological signs of children with *ABCA3* gene mutations overlap with those seen in other disorders of surfactant metabolism (*SFTPB* and *SFTPC* mutations) [14].

Therapy

Treatment options in patients with *ABCA3* gene mutations and severe respiratory distress in the neonatal period include mechanical ventilation, exogenous surfactant replacement and the use of corticosteroids. No specific therapeutic interventions are available for patients with disorders of surfactant metabolism. Therefore therapeutic strategies in patients with *SFTPC* and *ABCA3* gene mutations are based on treatment protocols for chronic interstitial lung disease in children [9,11].

The treatment of our patient was based on therapeutic approaches that have been previously described in newborns with SFTPC deficiency [1,24,26,28]. The major aim of various therapeutic strategies is to suppress inflammation. To achieve this goal, glucocorticoids, macrolides and hydroxychloroquine, have been proposed. Thouvenin et al. studied the use of corticosteroids and corticosteroids plus azithromycin or plus hydroxychloroquine in 22 patients who had SFTPC deficiency. 4 of 22 children were asymptomatic after a period of about 3 years. Oxygen therapy was no longer needed in 12 other children, however, a moderate dyspnea persisted [26].

The literature shows that strategies used to treat chronic interstitial lung disease have been successfully applied in children with mild clinical courses of *ABCA3* gene mutation [10]. Corticosteroids appear to increase the expression of ABCA3, at least in vitro. This hypothesis supports the therapeutic trial with corticosteroids. Clinical data that support the efficiency in case of proven ABCA3 deficiency are sparse [30].

As well, macrolides have been shown in a few reports in the literature, to induce a beneficial effect on chronic interstitial lung disease based on its anti-inflammatory effects. Clement et al. described the case of a child with *ABCA3* gene mutation who was treated with corticosteroids after onset of symptoms in the neonatal period until the age of 6 years. After a few weeks of treatment with azithromycin, the general condition improved significantly and the child did not require supplemental oxygen anymore [10]. Flamein et al. reported 3 children with neonatal respiratory distress harboring homozygous and compound heterozygous *ABCA3* gene mutations who developed chronic lung disease. They were treated with methylprednisolone pulse therapy for 14 months (patient 1), 6 years (patient 2) and 11 years (patient 3). In addition, they received azithromycin over 2 years (patient 1 and 3) and over 12 years (patient 2). Patient 1 did not require supplemental oxygen therapy. Patient 2 no longer required oxygen supplementation after 10 years. Patient 3 was still under oxygen therapy at the time of publication [16].

Ciantelli et al., however, described a newborn who had severe RDS (compound heterozygous mutation of the *ABCA3* gene of 2 new variants), in whom recurrent surfactant application and cortisone treatment achieved no positive effect [8].

In our patient with homozygous *ABCA3* gene mutation neither the modulation of inflammatory response by corticosteroids, hydroxychloroquine and macrolides nor any other therapeutic drug strategy exerted a positive effect on the clinical course (**Fig. 2**).

A lung transplant is the only option to prolong the survival of patients with fatal *ABCA3* gene mutations. There are only a few individual case reports of children with *ABCA3* gene mutation and successful lung transplants [15]. 9 children under 12 months of age with confirmed *ABCA3* gene mutation were described, who were transplanted from 1992 to 2007 in a lung transplant center in St. Louis, USA. The 5-year survival of children with surfactant protein disorders who have received a transplant is indicated in the literature as approximately 50% [15,23]. Mortality is often determined by infections, the occurrence of bronchiolitits obliterans and the development of lymphoproliferative malignancy. Since 1997 less than 10 lung transplants per year have been performed in infants worldwide. In Europe, lung transplants are only performed in rare cases in children younger than 2–3 years of age with a chronic or acute but irreversible respiratory insufficiency [20]. Donor organ shortage, limited number of centers, reduced quality of life after lung transplantation, and a high 5-year mortality rate of 50% in face of the young age limits the application of this option [18]. In the case of our patient, this therapeutic option was dismissed after extensive evaluation and discussion with the parents.

Conclusion

Mutations of the *ABCA3* gene are a rare differential diagnosis of RDS in the newborn period. The clinical course of patients with different *ABCA3* gene mutations is highly variable. There is a need for more experience in the treatment of newborns with *ABCA3* gene mutation. Courses, treatment and outcome of patients should be systematically collected in a patient registry. The Children's Lung Register (www.klreg.eu) or the ESPED survey (survey unit for rare pediatric diseases established in Germany) are available. In the current survey, which has been conducted since 7/2011, late pre-term and term newborns with severe neonatal respiratory failure with the need for additive therapy, such as surfactant administration, iNO inhalation, HFO ventilation or extracorporeal membrane oxygenation (ECMO), are included. As part of an EU-funded project dating from 2013 (www.child-EU.net), interstitial lung diseases should not only be observed, but also the randomized and controlled therapy strategies should be systematically investigated. This strategy would allow to accumulate knowledge about the effectiveness of drug interventions in this extremely rare disease with highly variable phenotypes due to the large number of different genetic changes.

Conflict of interest: The authors have no conflict of interest to disclose.

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