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PERINATAL/NEONATAL CASE PRESENTATION

Successful treatment of neonatal respiratory failure caused by a novel surfactant protein C p.Cys121Gly mutation with hydroxychloroquine

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SFTPC (surfactant protein C) mutations resulting in SP-C deficiency causing ongoing respiratory failure in the neonatal period represent a rare entity. We report a full-term female infant who developed respiratory distress and respiratory failure shortly after birth. From the first day of life the infant was mechanically ventilated. Application of exogenous surfactant or cortisone did not lead to any clinical improvement. Genetic analysis identified a novel *SFTPC* mutation as the cause of her lung disease. The patient was diagnosed as heterozygous for a p.Cys121Gly/C121G substitution encoded by exon 4, which could not be detected in both parents. Experimental therapy with hydroxychloroquine resulted in a significant clinical improvement within 2 weeks time. Mechanical ventilation was no longer needed, and the patient was discharged without additional oxygen demand. The patient remained well under therapy till the age of 6 months. After that time, the therapy was successfully discontinued.

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INTRODUCTION

Pulmonary surfactant is a mixture consisting of lipids (mainly phospholipids) and at least four specific surfactant proteins (SFTPs), SP-A, SP-B, SP-C and SP-D, which are synthesized by type II alveolar pneumocytes. In particular, the two hydrophobic proteins SP-B and SP-C reduce surface tension by interacting with the lipids to form a surface-active film at the air/liquid interface of the alveoli, thereby preventing the end-expiratory collapse of the alveoli and terminal bronchioles.

Hereditary SP-B deficiency is a well-established cause of severe respiratory failure in newborns. Currently there are 28 different *SFTPB* mutations known. In contrast to the *SFTPB* mutations, the clinical presentation and outcome of lung disease associated with *SFTBC* mutations is more variable. Although the majority of subjects are affected and show symptoms of interstitial lung disease later in life, case reports of neonates with severe respiratory failure have been published. Currently, there is no specific therapy for SP-C deficiency.

CASE

The female patient was born via primary cesarean section due to a disproportion at the gestational age of 39 + 2 weeks with a birth weight of 4320 g. The pregnancy was unremarkable. In particular, there were no signs of gestational diabetes. APGAR scores were 9 at 5 and 10 min due to mild grunting.

As the patient increasingly developed respiratory distress symptoms immediately after birth, she had to be transferred to the neonatal intensive care unit. Continuous positive airway pressure was initiated and antiinfectious therapy was started. Chest radiography demonstrated bilateral diffuse granular opacities(Figure 1). Within the first 24 h, the patient went into respiratory insufficiency with CO_2 retention and increasing oxygen demand, therefore leading to mechanical ventilation. The oxygen demand stayed at a level of more than 50% with a lack of response to the application of exogenous surfactant (porcine lung lavage). From day 3 onward, the patient was ventilated with a high-frequency oscillation ventilation. A second dose of exogenous surfactant did not improve her condition. Multiple arterial blood gas analyses revealed hypoxia and respiratory acidosis (for example, on day 5: PaO_2 62 mm Hg, $PaCO_2$ 72 mm Hg, pH 7.25). On day 7 a course of hydrocortisone was administered (2 mg/kg for 3 days, 1 mg/kg for 3 days,) with again no improvement of the pulmonary situation. Echocardiography showed reduced cardiac output resulting in the patient receiving dobutamine until day 10 of life. Tracheal aspirates were examined for viral, bacterial or fungal infections with negative results.

Because of the severe lung disease, evaluation for surfactant dysfunction was performed. No *SFTPB* mutations were identified. *ABCA3* was not examined, while *SFTPC* analysis revealed a novel missense mutation in exon 4. The patient was heterozygous for a $cysteine_{121}$ (TGC) → glycine (GGC)/p.Cys121Gly/C121G substitution. To clarify the relevance of this amino acid exchange, both parents were also analyzed and the mutation could not be detected. In the meantime, the respiratory situation of the patient deteriorated, requiring increasingly higher respiratory parameters (oxygenation index 30). A computer tomography of the chest at 4 weeks of life demonstrated a diffuse ground glass pattern with intra-alveolar alterations (Figure 2).

After confirmation of the *SFTPC* mutation, an experimental therapy with oral hydroxylchloroquine at a dose of 10 mg/kg per

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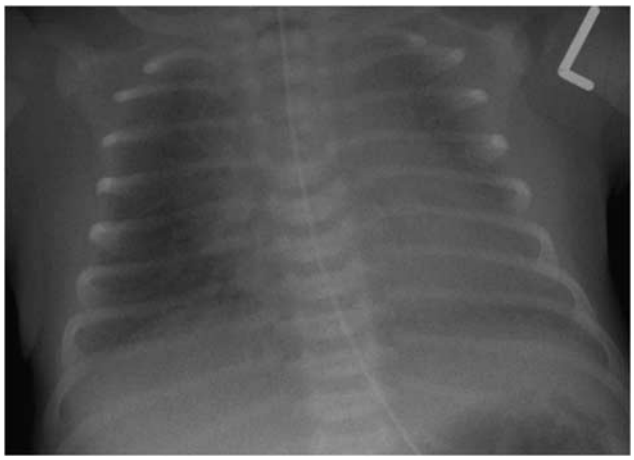

Figure 1. Bilateral diffuse granular opacities 4 h after birth.

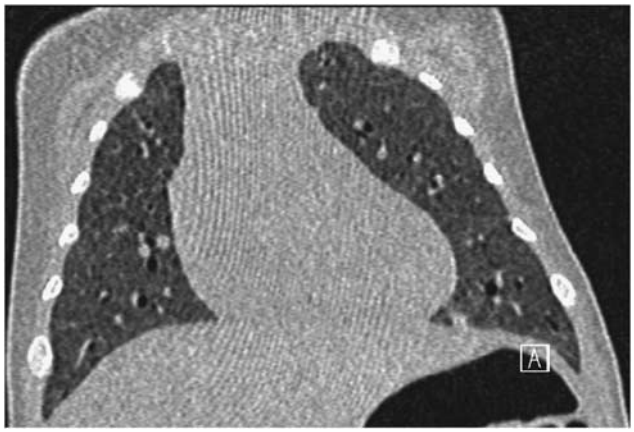

Figure 2. Diffuse ground glass pattern with intra-alveolar alterations at day 28.

day was initiated on day 23 after obtaining informed consent. Within 2 weeks, the respiratory situation improved continuously, so that the patient could be extubated at day 36. From day 47 onwards, she was without non-invasive ventilation and additional oxygen demand (Figure 3). After recovering from opioid withdrawal, she was discharged at day 70. Passive respiratory syncytial virus immunization was carried out. At 6 months of age, hxdroxychloroquine therapy was discontinued under careful supervision of the breathing pattern, respiratory rate and oxygen saturation. During the next 3 months, no change in the situation occurred. The respiratory rate, taken by her parents every evening after the patient was asleep, declined from an average of 30 per minute to 26 per minute. The patient showed a normal psychomotor development. Even upper airway infections did not exacerbate her pulmonary situation.

DISCUSSION

Surfactant protein C deficiency was first described in 2001[1] with varying clinical outcome. Most affected individuals show the clinical picture of chronic lung disease. However, case reports of severe neonatal lung disease are in existence.[1–3]

SFTPC mutations result in the production of misfolded pro SP-C that accumulates within cellular secretory pathways in the alveolar cell type II, resulting in the activation of cell stress responses and subsequent cellular injury and apoptosis.[4] Accordingly, the mutations identified so far are predominantly substitutions of

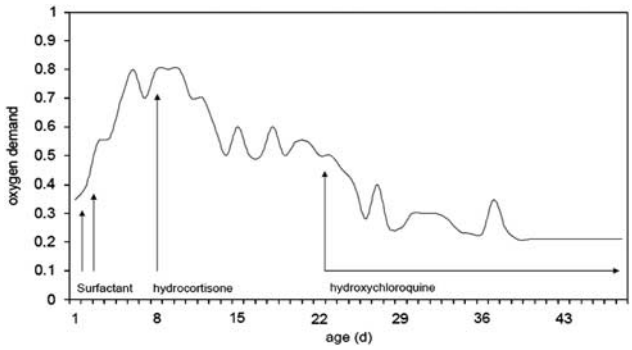

Figure 3. Oxygen demand in response to treatment.

highly conserved residues especially in the carboxy-terminal region of the protein, the so-called Brichos domain (amino acids 94 to 197). This domain presumably has chaperone activity, sustaining the alpha helical structure of the transmembrane domain and, by doing so, preventing the self-aggregation of SP-C before it is able to form a surfactant together with other proteins and phospholipids. Nevertheless, the most common SP-C alteration is an isoleucine (ATT)-to-threonine (ACT) exchange at position 73 of the protein.

The C121G replacement has not been reported previously. However, a very similar mutation at the identical position, a cysteine$_{121}$ (TGC)→phenylalanine (TTC)/p.Cys121Phe/C121F substitution, resulted in severe respiratory insufficiency with long-time mechanical ventilation in two patients (Griese and Lohse, unpublished data). In addition, replacement of cysteine$_{122}$ by glycine rat SP-C resulted in misfolding and non-lysosomal compartments, forming stable aggregates targeted for proteasomal degradation.[5]

Although lung transplantation may be an option in progressive respiratory failure,[6] currently there exists no standard therapy for respiratory failure due to SP-C deficiency. Replacement of external surfactant provides only a transient improvement in gas exchange and is largely ineffective in SP-B deficiency.[7] Rosen and Waltz[8] reported successful treatment of a 5-month-old boy with chronic lung disease due to SP-C deficiency with hydroxychloroquine. The mechanism of action may be a mixture of the drug's antiinflammatory properties[9] and a possible inhibition of the intracellular processing of the precursor of SP-C.[10]

According to our knowledge, this is the first case report of a severe neonatal respiratory failure due to SP-C deficiency in a neonate who was recovering under hydroxychloroquine therapy. However, a direct relationship between this treatment and the child's clinical improvement cannot be proven, but the close temporal association strongly suggests a causal role of this drug. Additional work is nevertheless needed to assess the general usefulness of hydroxychloroquine in patients with SP-C deficiency. In the setting of rare diseases, this goal can only be achieved by including patients in randomized trials within the frame of web-based registries.[11]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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