CASE REPORT

Successful weaning from mechanical ventilation in a patient with surfactant protein C deficiency presenting with severe neonatal respiratory distress

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SUMMARY

The clinical course and treatment in the first 2.5 years of life of a term-born girl with a severe onset of respiratory symptoms in the neonatal period caused by a p. Cys121Phe/C121F mutation in the gene of surfactant protein C (*SFTPC*) is described. During the first 9 months of life, she was mechanically ventilated. With methylprednisolone pulse therapy and oral prednisolone, she could eventually gradually be weaned from mechanical ventilation. At the age of 2.5 years, she is in a good clinical condition without any respiratory support and has a normal nutritional status and neurodevelopment. This clinical course with neonatal onset of respiratory insufficiency is remarkable since most patients with SFTPC mutations present with milder respiratory symptoms in the first years of life.

BACKGROUND

Respiratory diseases caused by inherited disorders of the surfactant metabolism are quite rare.[1] One of these disorders is surfactant protein C (SFTPC) deficiency in which the severity and course in time may be variable. Most patients present with mild respiratory symptoms in the first years of life, where only a minority presents in the neonatal period.[2] The variability in severity and course in time makes assessment of the prognosis for an affected individual very difficult. There is no established curative treatment available for inherited disorders of surfactant metabolism besides lung transplantation. In this case report, we describe a patient with a severe and early onset of respiratory symptoms with a remarkable improvement after months of mechanical ventilation and treatment with steroids.

CASE PRESENTATION

The patient's parents were non-consanguineous and healthy with no family history of respiratory disease. After an uncomplicated pregnancy with induction of labour at a gestational age of 41 weeks and 1 day, a baby girl was born with a birth weight of 3755 g. Apgar scores were 8 and 9 at 1 and 5 min, respectively. Within 24 h after birth, she developed signs of respiratory distress and increased oxygen demand for which she was treated with oxygen, nasal continuous positive airway pressure (CPAP) and antibiotics. On the fourth day after birth, the clinical condition worsened with increasing respiratory distress, for which she was intubated and received conventionally pressure-controlled ventilation. She received two doses of surfactant with only a transient improvement in oxygenation. Echocardiography showed a structurally normal heart with little signs of pulmonary hypertension for which a nitric oxide (NO) trial was performed with little effect. X-ray of the lungs revealed an increased whitening of the lungs consistent with respiratory distress syndrome (RDS). Bacterial and viral cultures were negative. After a trial with furosemide, she was extubated at the age of 2 weeks and received respiratory support by nasal CPAP and supplemental oxygen (FiO_2 30–40%). She remained in respiratory distress and her clinical condition worsened again for which she was reintubated and again received conventionally pressure-controlled ventilation. This time, it was not possible to wean her from mechanical ventilation. Meanwhile, mechanical ventilation was complicated by oxygenation problems and carbon dioxide retention for which mechanical ventilation had to be adjusted. Neither a switch to high frequency oscillation (HFO) nor the change to an endotracheal tube with a larger diameter significantly increased the respiratory condition of the girl. A high-resolution CT (HRCT) of the lungs at the age of 3 weeks showed patchy areas of ground glass attenuation with thickening of interlobular septae also called 'crazy paving' pattern (figure 1). Bronchoalveolar lavage (BAL) showed signs of active inflammation with infiltration of granulocytes and alveolar macrophages. An open lung biopsy at the age of 7 weeks revealed a pattern of interstitial pneumonitis. Hydroxychloroquine was started as an antiinflammatory agent because the HRCT was consistent with interstitial lung disease but did not have any effect. At the age of 3 months, she was still on mechanical ventilation with high settings (peak inspiratory pressure (PIP): 35 cm H_2O, positive end expiratory pressure (PEEP) 10 cm H_2O, FiO_2 45%) and unable to wean despite permissive hypercapnea and treatment with hydrocortisone. She was transferred to a hospital with expertise in pulmonary lavages in young children as a treatment option for alveolar proteinosis, the diagnosis which was suspected at that time.[3] After two sessions of pulmonary lavages without improvement, the child was referred back. DNA sequence analysis of the *SFTPB* and *ABCA3* genes were negative at that time. A later *SFTPC* gene analysis revealed that she was a heterozygous carrier of a p.Cys121Phe/C121F mutation encoded by exon 4. At the age of 4.5 months, a tracheostoma was placed because a

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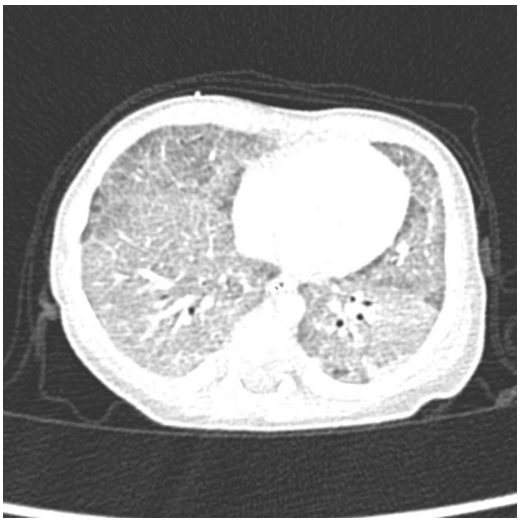

Figure 1 High resolution CT (HRCT) of the lungs at the age of 3 weeks showing patchy areas of ground glass attenuation with thickening of interlobular septae also called 'crazy paving'.

long period of mechanical ventilation was expected. After the tracheostoma was placed, sedation could be stopped which was important because of its negative effect on neurodevelopment and to improve further weaning from mechanical ventilation. Treatment with azithromycin was started for its immunomodulatory function. Corticosteroids were started again, consisting of methylprednisolone pulse therapy (300 mg/m^2/day intravenously during 3 days) and oral prednisolone 2 mg/kg/day. Initially, the methylprednisolone pulse therapy was started with 3-week intervals. Later, the frequency was decreased to every 4–5 weeks. After starting corticosteroids, ventilator settings and oxygen need substantially decreased, and the girl could be weaned from mechanical ventilation. At the age of 9 months, she was ventilated with pressure support ventilation with mild settings (PIP14 cm H_2O, PEEP 6 cm H_2O, FiO_2 25%). To wean the girl further from mechanical ventilation, ventilator-free intervals were started and increased to a maximum of 4 h a day

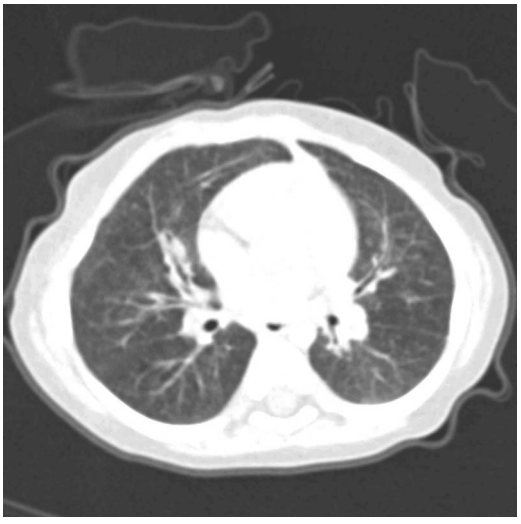

Figure 2 High resolution CT (HRCT) of the lungs at the age of 21 months showing an improvement of the ground glass aspect.

in which supplemental oxygen was given by nasal cannula. With this ventilator setting, she was discharged from the hospital with home mechanical ventilation. After discharge, she could be further weaned from mechanical ventilation and is without respiratory support or chronic supplemental oxygen since the age of 18 months. The oral prednisolone was tapered, and after 4 months substituted by oral administration of hydrocortisone in an equivalent dosage which was further reduced over time and stopped at the age of 19 months. Methylprednisolone therapy was stopped 1 month after complete weaning from mechanical ventilation. A HRCT of the lungs at the age of 21 months showed an improvement of the ground glass aspect (figure 2). The girl was initially fed with normal formula through a gastric tube which was well tolerated. Because of feeding intolerance along with vomiting, mucous diarrhoea and poor weight gain, the normal formula was switched to an elemental formula on the suspicion of a cow milk allergy. After the switch to this elemental formula, her stools normalised and her weight gain was satisfactory. Because of prolonged feeding through a nasogastric tube at the age of 8 months, a percutaneous endoscopic gastrostomy (PEG) tube was placed. During the second year of life, oral feeding was introduced and gastric tube feeding could be stopped. Despite the severe clinical course with prolonged mechanical ventilation and treatment with systemic corticosteroids, her length growth and weight gain are within the normal range. Before discharge, a cerebral MRI was made at the age of 9 months, which showed delayed myelination probably caused by the treatment with systemic corticosteroids during a prolonged period of time. There was also a significant neurodevelopmental delay mainly caused by the prolonged mechanical ventilation and accompanying sedation. After discharge, she was treated by a multidisciplinary rehabilitation team, and her neurodevelopment increased in time. A detailed neurological examination at the age of 2.5 years showed a completely normal neurodevelopment.

OUTCOME AND FOLLOW-UP

At the age of 2.5 years, the girl is in a good clinical condition without marked signs of respiratory distress and without chronic demand of supplemental oxygen. She is currently orally fed with a cow milk-free diet. Her length growth and weight gain are within the normal range. On detailed neurological examination, she showed normal neurodevelopment.

DISCUSSION

Surfactant is a complex mixture of phospholipids and proteins consisting of four surfactant-associated proteins and is produced by alveolar type II cells. Surfactant proteins A and D are hydrophilic proteins and contribute to the host defence in the lung, whereas surfactant proteins B and C are hydrophobic proteins which reduce surface tension, and thus prevent alveolar collapse.[4] The first mutation in the *SFTPC* gene was described in 2001.[5] Currently, over 35 dominantly inherited SFTPC mutations have been described in association with acute and chronic lung diseases in patients.[6] The genetic defects result in a disruption of the normal processing of pro-SPC to mature SPC. Depending on the site of the mutation, misfolded pro-SPC, reduced or no mature SPC are produced. Precursors of SPC may accumulate in alveolar type II cells, resulting in an activation of cell stress responses and subsequent cellular injury and apoptosis.[7] In contrast to patients with mutations on SFTPB who usually present in the neonatal period with acute and severe respiratory symptoms, patients with SFTPC mutations mostly present with respiratory symptoms later in life. The clinical course in these patients may be variable over

time with some patients having persisting chronic respiratory problems which may improve and resolve, but others require lung transplantation, and some ultimately succumb.[2] This variability in severity and course of the disease makes assessment of the prognosis for an affected individual very difficult. In every term newborn with an unexplained respiratory distress in the first week of life, which requires mechanical ventilation without clear improvement and no obvious cause of disease, an evaluation for inherited disorders of surfactant metabolism should be considered. The steps in this diagnostic approach heavily rely on genetic testing and, if inconclusive, lung biopsy.[8] HRCT of the lungs and analysis on BAL fluid may give some more hints into the direction of an interstitial lung disease; however, these will not be genetically diagnostic. After establishing the diagnosis, consultation with or referring to an expertise centre is advisable in particular since there is no established curative treatment for inherited disorders of surfactant metabolism available besides lung transplantation. Besides long-term respiratory support and supplemental oxygen, hydroxychloroquine and corticosteroids are used in patients with interstitial lung disease. They may provide some improvement because of their anti-inflammatory effects and the inhibitive role of hydroxychloroquine in the intracellular processing of pro-SPC, but have not been systematically evaluated.[9] There are very few case reports with such a severe and neonatal onset of respiratory failure due to a SFTPC mutation. The patient described by Soraisham *et al*[10] was mechanically ventilated, and treated with dexamethasone and repeated surfactant replacement therapy. The child died on day 44 because of unremitting hypoxaemia for which ventilator management was withdrawn. Poterjoy *et al*[11] described a patient who was mechanically ventilated until the age of 20 months when she underwent a bilateral lung transplantation. After the lung transplantation, the child was weaned from mechanical ventilation and discharged home at the age of 23 months. Recently Hepping *et al*[12] described a patient who was mechanically ventilated from the first day of life and treated with exogenous surfactant and cortisone without any clinical improvement. After treatment with hydroxychloroquine, the respiratory condition improved within 2 weeks so that the patient could be extubated. Our patient had a severe and early onset of respiratory symptoms with a remarkable improvement after months of mechanical ventilation and especially treatment with steroids. Hydroxychloroquine did not improve her respiratory condition.

In conclusion, in this paper, we described the clinical course and treatment of a girl with an early and severe onset of respiratory symptoms caused by a novel p.Cys121Phe/C121F mutation of the SFTPC gene. This case illustrates that in every patient with unexplained respiratory distress without improvement in time and signs of interstitial lung disease on HRCT scan, genetic disorders of the surfactant metabolism should be considered. Consultation and collaboration with experts in the evaluation of children with disorders in surfactant metabolism is important to collect experiences made in individual cases. This is possible with the help of website http://www.kids-lung-register.eu. In order to improve outcome in the future, patients should be followed and treated in prospective studies, available now in Europe (http://www.childeu.net).

Learning points

- In every patient with unexplained respiratory distress without improvement in time and signs of interstitial lung disease on HRCT scan, genetic disorders of the surfactant metabolism should be considered, although they are quite rare.
- Most patients with a SFTPC deficiency present with mild respiratory symptoms in the first years of life; however, neonatal and severe onset, as in our patient, is described.
- In contrast to patients with SFTPB deficiency, patients with SFTPC deficiency can be successfully weaned from mechanical ventilation with treatment of systemic corticosteroids.
- Consultation and collaboration with experts in the evaluation of children with disorders in surfactant metabolism is important to collect experiences made in individual cases. Patients should be followed and treated in prospective studies in order to improve outcome in the future.

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