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CLINICAL CASE

Surfactant protein C dysfunction in pediatric patients: Clinical Case

Disfunción de la proteína surfactante C en pacientes pediátricos: Caso Clínico

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What do we know about the subject matter of this study?

Surfactant protein C dysfunction is a rare diffuse interstitial lung disease that causes significant mortality in children due to the respiratory complications to which they are susceptible.

What does this study contribute to what is already known?

In our series, the age at the onset of this disease varied and responded to treatment similar to other published reports. The clinical, radiological, and histological characteristics and lamellar ultrastructure can guide the diagnosis of surfactant protein C dysfunction.

Abstract

Pulmonary surfactant dysfunction disorders are caused by genetic defects that alter pulmonary surfactant metabolism. They are rare disorders and cause significant morbidity and mortality in the neonatal and pediatric populations. **Objective:** To describe the clinical, histopathological, and ultrastructural findings of the lamellar body that suggest surfactant protein C (SP-C) dysfunction, where confirmatory genetic studies are not available. **Clinical Case:** We report three pediatric cases of pulmonary surfactant dysfunction disorders from a pediatric hospital in Peru. Video-assisted lung biopsy was performed in all cases. Ultrastructural studies of the lamellar body were compatible with type-C pulmonary surfactant dysfunction. The treatment used was methylprednisolone pulses monthly for six months, then every two months, varying the duration according to the clinical evolution. They also received daily hydroxychloroquine and azithromycin three times a week. Clinical evaluations, eye fundus, echocardiogram, electrocardiogram, and biochemistry were performed periodically. At

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follow-up, there was a good response to treatment and no adverse effects were observed. One case died despite the therapies received. **Conclusions:** In 3 patients with type-C surfactant dysfunction, treatment with corticosteroids, hydroxychloroquine, and azithromycin was successful in 2 of them. This is one of the first case series reported in Peru that contributes to the study of these diseases, especially in low- and medium-income countries.

Introduction

Pulmonary surfactant is a molecular complex of lipids and proteins located at the air-liquid interface of the pulmonary alveoli whose main function is to decrease surface tension, prevent alveolar collapse at the end of expiration, and regulate gas exchange[1,2].

Proteins represent 10% of the pulmonary surfactant weight. The hydrophilic surfactant proteins type A (SP-A) and type D (SP-D) play an important role in pulmonary innate and adaptive immunity. Hydrophobic surfactant proteins type B (SP-B) and type C (SP-C) stabilize the surfactant film on the alveolar surface and enhance lung innate immunity and lung surfactant catabolism[2,3]. The ABCA3 transporter, thyroid transcription factor (NKX2-1), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are also components of the normal surfactant structure and function[2-4].

Pulmonary surfactant dysfunction disorders are a group of rare diseases within the group of children's interstitial and diffuse lung diseases (ChILD), caused by genes mutations that synthesize surfactant proteins and cause significant morbidity and mortality in late preterm, term infants, and children[1,5,6]. Genetic variations have been described mainly in genes encoding SP-C and ABCA3, less frequently in genes encoding NKX2-1, SP-B, SP-A, and GM-CSF receptors[2].

The course of the disease is highly variable, with some presenting with severe respiratory failure in the neonatal period requiring lung transplantation; while others have chronic interstitial lung disease requiring long-term oxygen therapy and another group remains relatively asymptomatic[4].

Histopathology of SP-C dysfunction shows diffuse alveolar damage, lymphocytic inflammation, muscularization of alveolar septa, foamy alveolar macrophages, and type II pneumocyte hyperplasia[1,7]. It is also associated with histopathological patterns of neonatal pulmonary alveolar proteinosis (PAP), nonspecific interstitial pneumonitis (NSIP), desquamative interstitial pneumonia of infancy (DIP), and chronic pneumonitis of infancy (CPI). Likewise, electron microscopy shows intracellular membranous aggregates, large lamellar bodies of normal appearance with electro-dense vesicles, and compound and disorganized lamellar bodies[1,7].

Treatments for SP-C dysfunction are limited and nonspecific and, for most patients, lung transplantation is the only option for survival, even with a high risk of complications and mortality[8].

The objective of this work is to describe the clinical, histopathological, and ultrastructural findings of the lamellar body that are indicative of SP-C dysfunction, where confirmatory genetic studies are not available.

Clinical Case

Case 1

One-year-old female infant presented for consultation due to a one-week history of marked respiratory distress associated with fever. She had no previous illnesses, no hospitalizations, and no complications during pregnancy and delivery. On the physical examination, she had a respiratory rate of 60/min, multiple intercostal retractions, diffuse crackles in both hemithorax, and 67% of oxygen saturation (FiO2 21%). Blood cultures, study for suspected congenital diseases (TORCH), blood immunoglobulin measurement, and flow cytometry to evaluate lymphocyte population were normal. A chest X-ray showed bilateral reticular interstitial opacities and a chest CT scan showed a diffuse reticular pattern and subpleural ground-glass opacities (Figure 1A and 1B). Histopathology and electron microscopy of lung biopsy were suggestive of SP-C dysfunction (Figure 1C, 1D, and 1E).

Treatment with methylprednisolone pulses was initiated at 30mg/kg/day dose for three days, receiving 12 monthly cycles and then 12 more cycles every two months. Oral hydroxychloroquine at 5mg/kg/12h dose and azithromycin at 10 mg/kg/48h dose were included, both permanently. With the treatment, her tachypnea decreased, although it did not normalize so she required long-term oxygen therapy at 4 L/min, which was progressively decreased until its use was discontinued. The patient was periodically evaluated in outpatient consultation for monitoring the progress of the disease and administration of methylprednisolone cycles. She had two brief hospital admissions due to viral respiratory infections, requiring management for wheezing, and one admission due to severe viral pneumonia requiring management in the intensive care unit.

She had periodic electrocardiograms and eye fundus checks, which were normal. Currently, the patient is six years old and has remained clinically stable without requiring oxygen.

Case 2

Five-year-old female schoolchild with a history of prematurity (31 weeks) and focal segmental glomerulosclerosis diagnosed at four years of age with multiple hospitalizations due to renal complications. At five years of age, she was referred to our institution due to pneumonia that did not improve with antibiotic treatment. On the physical examination, she had a respiratory rate of 70/min, 80% of oxygen saturation (FiO2 21%), clubbing, intercostal retractions, and diffuse crackles on pulmonary auscultation. Blood cultures, immunoglobulin profiles, and flow cytometry were performed to evaluate the lymphocyte population, all within normal ranges. A chest X-ray showed bilateral reticular interstitial opacities and a chest CT scan showed a reticular pattern and diffuse ground-glass opacities with bronchial wall thickening (Figure 2A and 2B). Due to persistent hypoxemia, a lung biopsy was performed, which showed histopathologic and ultrastructural findings suggestive of SP-C dysfunction (Figure 2C, 2D, and 2E). The echocardiogram showed moderate to severe pulmonary hypertension.

Treatment was started for 3 days with methylprednisolone at 30mg/kg/day dose, hydroxychloroquine at 5mg/kg/12h dose, azithromycin at 10mg/kg/48h dose, and sildenafil at 1mg/kg/8h dose for one month. There was little clinical improvement and she required long-term oxygen therapy at 3 L/min. Despite treatment, she died one month after admission due to respiratory failure.

Case 3

Preterm male infant, 45 days old, born by normal

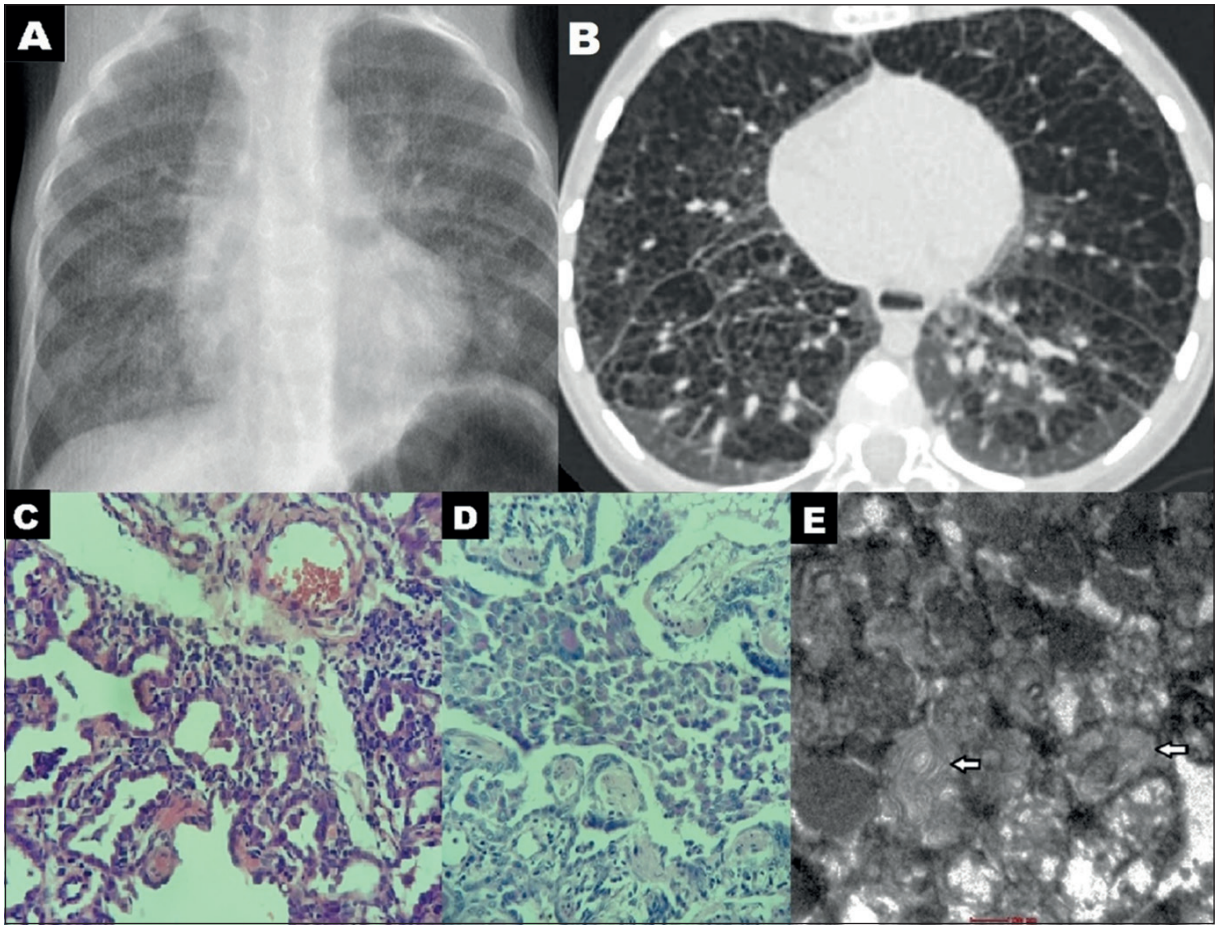

Figure 1. A: Chest X-ray. Bilateral diffuse reticular interstitial opacities. **B:** Chest tomography in pulmonary window and axial plane. Bilateral diffuse reticular pattern and with subpleural ground glass opacities predominantly in the lower lobes. **C:** Prominent alveolar epithelial hyperplasia, presence of foamy alveolar macrophages and interstitial lymphocytic infiltrate (Hematoxylin-Eosin stain) (Magnification x 200). **D:** Positive PAS stain for alveolar proteinaceous material (Periodic Acid Schiff or PAS stain) (Magnification x 400). **E:** In the ultrastructure by electron microscopy, two lamellar bodies are observed, decreased in number, increased in size and of normal appearance (arrows) (Bar size 200nm).

delivery, presenting marked respiratory distress since birth. He was referred to our institution at 20 days of life due to persistent respiratory distress that did not improve with oxygen therapy. On the physical examination, he had a respiratory rate of 70/min with multiple intercostal retractions, and 85% of oxygen saturation (FiO2 21%). Pulmonary auscultation showed diffuse crackles in both hemithorax. The rest of the clinical examination was normal. Laboratory tests for suspicion of congenital diseases (TORCH), and bacterial infections (blood cultures) were negative, as well as immunoglobulin measurement and flow cytometry to evaluate any primary immunodeficiency. A chest X-ray showed bilateral reticular interstitial opacities and a chest CT scan showed bilateral diffuse ground-glass patterns with areas of septal thickening (Figure 3A and 3B). Due to persistent hypoxemia, a lung biopsy was performed, which showed histopathology and ultrastructural findings suggestive of SP-C dysfunction (Figure 3C, 3D, and 3E).

Cycles of methylprednisolone at 30mg/kg/day dose for three days were initiated monthly, receiving six cycles and then six more cycles every two months. He also received hydroxychloroquine at 5mg/kg/12h dose and azithromycin at 10mg/kg/48h dose, both for 18 months. At two months and fifteen days, after the first pulse of methylprednisolone, oxygen therapy was withdrawn (he required 1 L/min to maintain adequate saturation). He had two brief hospital admissions due to viral infections. Currently, the patient is 3 years old, has outpatient check-ups, and is clinically stable.

Discussion

Genetic mutations encoding surfactant proteins cause significant primary lung disease in late preterm, term infants, and children. The mutation of these genes causes an alteration of surfactant function, leading

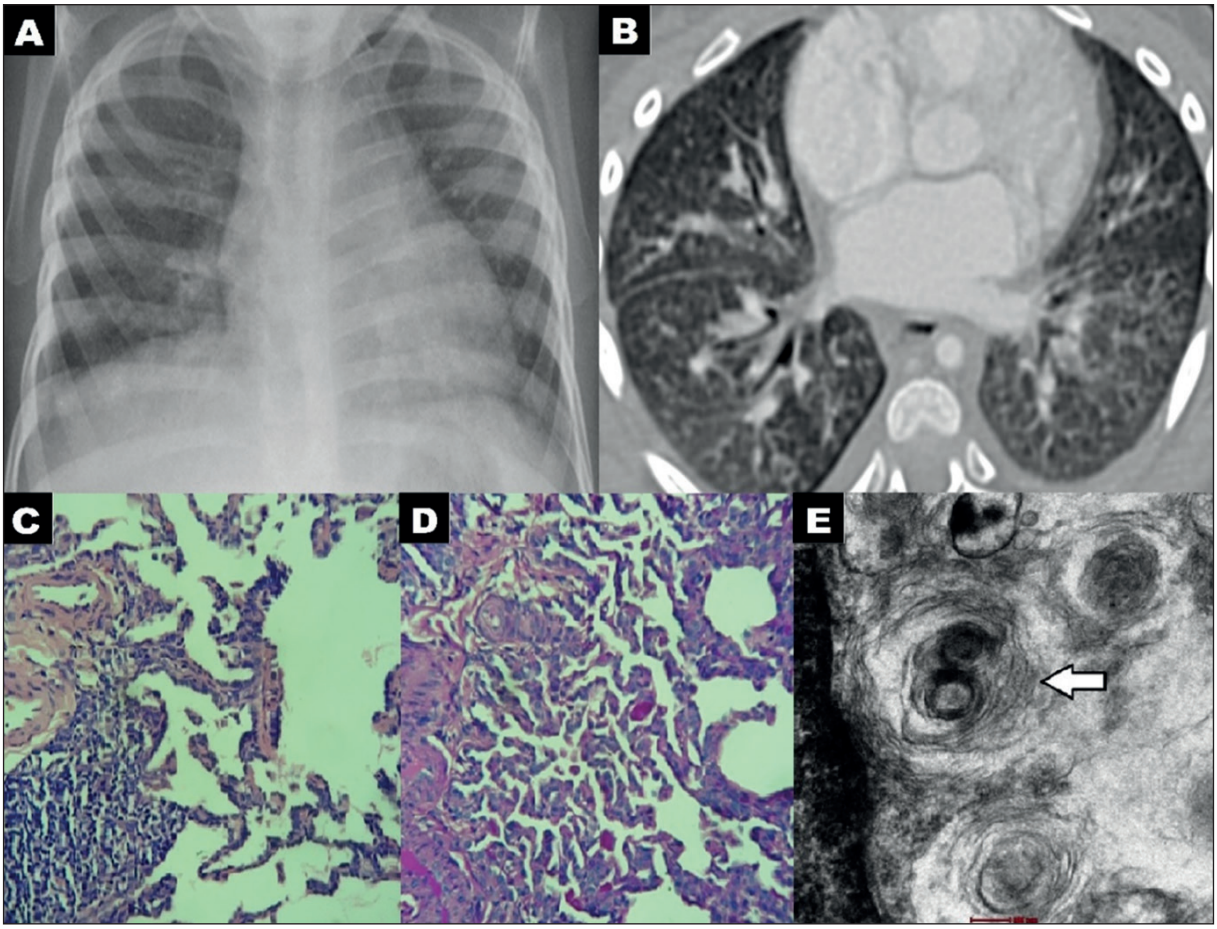

Figure 2. A: Chest X-ray. Bilateral reticular interstitial opacities. **B.** Chest tomography in pulmonary window and axial plane. Reticular pattern and diffuse ground-glass opacities with thickening of the bronchial wall. **C:** Prominent alveolar epithelial hyperplasia, variable interstitial expansion, few foamy alveolar macrophages, and presence of lymphoid accumulation (Hematoxylin-Eosin staining) (Magnification x 200). **D:** Positive PAS staining in foamy macrophages (Periodic Acid Schiff or PAS stain) (Magnification x 400). **E:** The electron microscopy image shows a large and compound lamellar body (arrow) (Bar size 700nm).

to histological changes that hinder gas exchange in the lung, resulting in chronic respiratory failure[8]. The genetic study is important to establish the specific diagnosis when there is suspicion of SP-C dysfunction; however, a clinical history of chronic respiratory distress, immunohistochemical examination, and ultrastructure of lung tissue are relevant for the diagnostic orientation of these disorders[1,9]. Genetic studies are not available in our country, however, the experience of the pediatric pulmonologist and the use of electron microscopy in recent years has improved the suspicion and diagnosis of this type of disease as seen in previous reports[10]. The prevalence of SP-C mutations is unknown as it is an autosomal dominant disease with a highly variable phenotype, with induction of endoplasmic reticulum stress, cytotoxicity, and apoptosis being possible mechanisms of disease[11].

The clinical presentation varies according to the gene affected. In SP-C dysfunction, the presentation of neonatal respiratory distress is well described and is not necessarily associated with a poor prognosis as in SP-B deficiency, however, the presentation can be at any age, and even delayed into adulthood[11,12]. In our series, the respiratory clinical manifestations started in the neonatal period (case 3) and during childhood (cases 2 and 3) (Table 1).

Chest X-rays findings in SP-C dysfunction include diffuse interstitial or alveolar infiltrates affecting all pulmonary lobes. In the CT scan, there is a ground-glass pattern, thickening of the interlobular and intralobular septa, parenchymal consolidation, occasionally subpleural cysts, and pulmonary nodules, and, with time, they can evolve into parenchymal cysts[11,13]. Pectus excavatum has also been reported in children as a musculoskeletal sequela in relation to changes in the development of

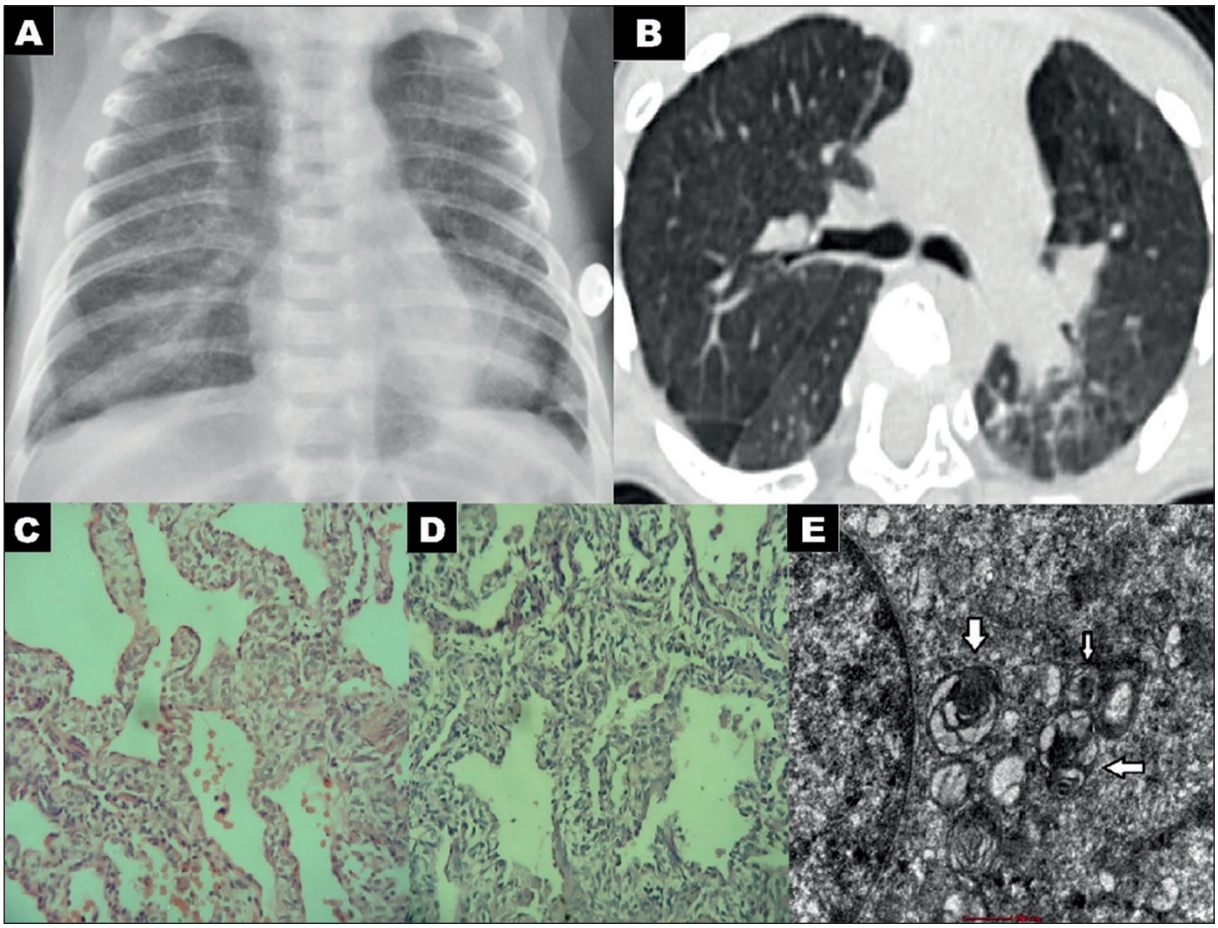

Figure 3. A: Chest X-ray. Bilateral reticular interstitial opacities. **B:** Chest tomography in pulmonary window and axial plane. Bilateral diffuse ground glass pattern with areas of septal thickening in left posterior segments. **C:** Alveolar epithelial hyperplasia with interstitial expansion, presence of few foamy alveolar macrophages and mild interstitial infiltrate (Hematoxylin-Eosin staining) (Magnification x 200). **D:** PAS stain highlights the few macrophages (Periodic Acid Schiff or PAS stain) (Magnification x 400). **E:** Electron microscopy where poorly shaped lamellar bodies are observed, with unstructured phospholipid membranes, other large ones with poorly identifiable and disorganized layers (large arrows), occasionally packed lamellar bodies without dense core are observed (small arrow) (Bar size 500nm).

the thorax due to chronic restrictive lung disease. In our series, only case 3 presented pectus excavatum. Likewise, in all cases, the chest X-rays showed diffuse reticular opacities, while in the CT scans, the ground-glass pattern and diffuse reticular pattern stood out (Table 1).

Lung biopsy may show histologic patterns indicative of a particular surfactant protein mutation when the genetic diagnosis is inconclusive, in cases where disease progression does not allow time for genetic studies, or when these are not available[11]. The most common histopathological patterns are desquamative interstitial pneumonitis (DIP), chronic pneumonitis of infancy (CPI), and nonspecific interstitial pneumonia (NSIP), all of which may overlap[1,5,14]. In our cases, lung biopsy showed histologic patterns of DIP and NSIP (case 1) and CPI (cases 2 and 3) (Table 1).

Electron microscopy reveals specific lamellar body abnormalities in cases of SP-C dysfunction and should be performed systematically because the information with conventional histology is limited. It also guides molecular and genetic studies for specific diagnoses of pulmonary surfactant dysfunction[1,5,7]. In our series, all three cases had electron microscopy studies of lung biopsy, which indicated SP-C dysfunction (Table 1).

A genetic study in surfactant dysfunction disorders allows greater prognostic certainty and adequate genetic counseling, however, it is not always available in low- and middle-income countries such as ours[10,15].

Given the infrequent presentation of pulmonary surfactant disorders, there are no randomized controlled trials on medical treatment in children and the current evidence derives from case reports, case series, and clinical observations and experiences[16,17]. In our series, all patients had chronic hypoxemia and required long-term oxygen therapy. When facing an acute picture with increased respiratory effort and hypoxemia, supportive measures may vary from oxygen therapy to noninvasive and even invasive ventilation. Nutritional status is also affected, and nutritional support should include long-term nutritional supplementation[12]. Most patients with these problems have intermittent hypoxic episodes, suboptimal nutrition, and impaired psychomotor development[18].

In our series, the treatments used were methylprednisolone pulses at 30 mg/Kg/day dose for three days, monthly for six months, and then every two months for as long as necessary, assessing symptom control. They also received hydroxychloroquine at 10mg/kg/day dose and azithromycin at 10 mg/kg/48h dose, which were very well tolerated and without significant side effects. Cases 1 and 3 remained stable with the established therapy and case 2 died due to respiratory failure despite the therapies received.

Variable responses to empirical therapies with hydroxychloroquine, azithromycin, and high doses of corticosteroids have been observed. It will depend greatly on the variety of mutations for some cases to develop pulmonary fibrosis and progress to lung transplantation or death despite medical therapy[19,20]. The dose of hydroxychloroquine at 10mg/kg/day, azithromycin at 10mg/kg three times per week, and response to treatment should be assessed after three months of treatment. Methylprednisolone should be started at 10mg/kg or 500 mg/m2 (some centers use 30mg/kg) daily for three consecutive days and repeated monthly for up to six months. Others opt to use prednisolone at 1mg/kg/day between methylprednisolone cycles or 2mg/kg/day of prednisolone instead of methylprednisolone cycles. Despite this, the responses to them are variable and, in all cases, the monitoring of side effects must be strict due to the prolonged use of these therapies[16,21].

The variable genotype-phenotype correlation makes necessary studies of genetic and environmental factors, functional studies of disease mechanisms, and randomized clinical trials of pharmacotherapeutics to explain prolonged survival without lung transplantation[22]. Lung transplantation is an option when end-stage pulmonary fibrosis develops, however, determining the exact moment is difficult because the natural evolution of the disease is poorly described and difficult to predict[17]. In European and North American centers combined heart and lung transplantation is performed in cases with poor response to treatment, however, mortality continues to be significant[18]. This encourages us to continue to value the contributions of pharmacological management in places with limited resources.

Gene therapy with genome editing or gene replacement strategies is a promising option to treat genetic disorders of SP-C, SP-B, and ABCA3 transporter dysfunction of pulmonary surfactant[4,11].

Finally, during the follow-up of our series, we observed clinical stability during the cycles with corticosteroids and adjuvant therapy with hydroxychloroquine and azithromycin. In case 1, treatment was discontinued after one year, however, subsequent clinical deterioration was evidenced, and corticosteroid cycles were restarted. Prolonged adjuvant therapy was maintained in all cases; however, the lack of solid clinical trials makes it difficult to know the true effectiveness of long-term medical therapy without neglecting its potential adverse effects.

In conclusion, the clinical, radiological, histopathological features, and lamellar body ultrastructure study of our series were compatible with SP-C dysfunction. These components allow us to orient toward the diagnosis of SP-C dysfunction in low- and middle-income countries such as ours, where genetic study is not available. The participation of a multidisciplinary team is important for the early diagnosis and treatment of these genetic lung diseases.

Table 1. Clinical, radiological, and histopathological characteristics of patients with lung surfactant dysfunction at the Instituto Nacional de Salud del Niño-Breña, Lima-Peru

	Case 1	Case 2	Case 3
Gestational age (weeks)	38	31	36
Birth weight (grams)	2710	900	2100
Sex	Woman	Woman	Male
Age of respiratory evaluation	1 y	5 y	1 m 15 d
Age at the time of lung biopsy	1 y	5 y 7 m	2 m
Clinical manifestations at admission	Tachypnea (RR 60/min) Respiratory distress SO2 67% FiO2 0.21 Crackles Digital hippocratism	Tachypnea (RR 70/min) Respiratory distress SO2 80% FiO2 0.21 Crackles Digital hippocratism Chronic malnutrition	Tachypnea (RR 70/min) Respiratory distress SO2 85 % FiO2 0.21 Crackles No Digital hippocratism Chronic malnutrition
Nutritional status at admission	Chronic malnutrition	Chronic malnutrition	Chronic malnutrition
General investigations	Negative study for congenital diseases, infectious diseases, and immunological profile.	Diagnosis of focal segmental glomerulosclerosis. Negative study for infectious diseases and immunological profile.	Negative study for congenital diseases, infectious diseases, and immunological profile.
Chest x-ray	Bilateral reticular interstitial opacities.	Bilateral reticular interstitial opacities.	Bilateral reticular interstitial opacities.
Thorax tomography	Diffuse reticular pattern and subpleural ground-glass opacities.	Reticular pattern and diffuse ground-glass opacities with thickening of the bronchial wall.	Bilateral diffuse ground glass opacities and thickening of the interlobular septum.
Echocardiogram	Normal	PSAP 60 mmHg (PHT)	PSAP 45 mmHg (PHT)
Histopathology	DIP, NSIP	CNI	CNI
Electron microscopy	Alveolar septa with elevated inflammatory cells and intracellular membranes. Pneumocytes II show large lamellar bodies, in smaller numbers and normal shape.	Some collapsed alveolar spaces. Some pneumocytes II have large and compound lamellar bodies.	Interstitium with many collagen fibers. Pneumocytes II have large lamellar bodies, in smaller numbers, poorly shaped, and some packaged without "dense core".

PASP: pulmonary artery systolic pressure. DIP: desquamative interstitial pneumonitis. NSIP: non-specific interstitial pneumonitis. CNI: chronic pneumonitis of infancy. PHT: pulmonary hypertension.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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