ABC3 Deficiency in a Newborn with Respiratory Failure

*Deficiencia de ABC3 en un recién nacido con insuficiencia respiratoria*

**Dear Editor,**

Congenital surfactant deficiencies are rare conditions, including mutation in the surfactant protein B (SP-B), surfactant protein C (SP-C) and ABC3 (ATP-binding cassette member A3) genes. They may present with respiratory failure and pulmonary hypertension (PH) in the newborn. Long-term outcomes are different according to the mutations.

We present an infrequent case, diagnosed in a tertiary hospital, who has survived.

A term female Arabian infant was born via spontaneous vaginal delivery. Mother and father were consanguineous. Immediately after birth, the infant developed respiratory distress and was initially managed with continuous positive airway pressure.

Her physical examination was notable for bilateral coarse breath sounds and generalized thoracic retractions. Chest radiograph demonstrated diffuse bilateral granular opacities. An echocardiogram revealed no evidence of anatomic heart disease with suprasystolic levels of pulmonary artery pressure. Over the next days, her gas exchange worsened, needing intubation and mechanical ventilation. She developed progressive hypoxic respiratory failure that needed high frequency oscillatory ventilation, and nitric oxide administration.

The infant was treated with antibiotics but infectious causes for PH were ruled out with negative blood cultures. Chest computer tomography (Fig. 1) at 15 days of life showed bilateral granular opacities and ground-glass opacification; two doses of surfactant were administered without improvement. Bronchoscopic bronchoalveolar lavage detected PAS positive material. With this information, a lung biopsy trough video thoracoscopy was performed. There were marked alveolar epithelial hyperplasia and mild widening of alveolar walls and the suspicion of a genetic disorder of surfactant dysfunction was considered. She still needed mechanical ventilation and take away a treatment with monthly high intravenous doses of methylprednisolone in association with oral daily hydroxychloroquine and every other day azithromycin.

Genetic testing showed a nonsense mutation in ABC3 gene, c.4681C>T or p.R1561X. This mutation was present on both maternal and paternal alleles.

At 7 months of age the infant was transferred to a pediatric lung transplant unit where she underwent bilateral lung transplantation at 10 months of age. Currently she is 2 years old needing home mechanical ventilation support because of tracheal and right main bronchus malacia.

Intersitial lung diseases (ILD) are a heterogeneous group of pathologic processes that affect pulmonary parenchyma and, in most cases, lead to an impairment of gas transfer and reduction of the lung capacity. There are no reliable estimates, but prevalence is likely <1 per 100,000.

**Table 1** Classification for ILD in Children.

<table>
<thead>
<tr>
<th>Diffuse developmental disorders</th>
<th>Acinar dysplasia, congenital alveolar dysplasia, alveolar-capillary dysplasia</th>
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<tr>
<td>Growth abnormalities</td>
<td>Pulmonary hypoplasia, structural pulmonary changes with chromosomal abnormalities</td>
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<td>Specific conditions of undefined etiology</td>
<td>Pulmonary interstitial glycogenosis, neuroendocrine cell hyperplasia of infancy</td>
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<td>Surfactant dysfunction mutations</td>
<td>SPFTB, SPFTC, ABC3 genetic mutations</td>
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<tr>
<td>Disorders of the normal host</td>
<td>Infectious processes, environmental agents, aspiration syndromes, eosinophilic pneumonia</td>
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<td>Disorders related to systemic disease processes</td>
<td>Immune-related disorders, storage disease, Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>Disorders masquerading as interstitial disease</td>
<td>Arterial hypertensive vasculopathy, congestive vasculopathy, lymphatic disorders</td>
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The definition requires at least three of the four following criteria in the absence of other know lung disorders: (1) respiratory symptoms (cough, rapid and/or difficult breathing, or exercise intolerance), (2) signs (resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) diffuse abnormalities on chest X-ray or CT scan. Thus, establishing 3 of 4 criteria is a sensitivity method for recognizing patients that could benefit from and ILD evaluation.

The earliest presentation of ILD is shortly after birth, with unexplained respiratory distress in a term neonate.

An organized classification scheme for ILD in children was published by the chiLD Research Network1-5 (Table 1).

Given the non-specific presentation of ILD, difficulty is frequently experienced in discerning ILD. Excluding these conditions prior to proceeding to more invasive test is important.1,2,6:

- **Infection screen.**
- An **echocardiography** to rule out structural cardiovascular disease and pulmonary hypertension.
- Baseline **chest X-ray.**
- Thin-section **CT** scanning. Ground glass opacification and air trapping are classical features detected.
- **Flexible bronchoscopy with BAL** to exclude infection or airway abnormalities.
- **Genetic testing.** Surfactant protein mutations produce recognizable clinical phenotypes of varying severity.
- **Lung biopsy** is the gold standard.

The gene for ABC3 is expressed in alveolar type II cells, and the protein is localized to lamellar bodies. ABC3 mutations have been associated with lethal neonatal respiratory distress and surfactant metabolism dysfunction. Outcomes in patients with ABC3 mutations are variable, ranging from severe irreversible respiratory failure in early infancy to chronic static or progressive ILD.7,8

There have been no controlled trials of therapeutic interventions in ILD syndrome. Case reports of improvement have been recorded with use of glucocorticoids, hydroxychloroquine, aza-thioprine, bronchodilators, mycophenolate, and other immune modulators.9,10 Lung transplantation is an option in end-stage lung disease.11

**Fig. 1.** CT with bilateral granular opacities and ground-glass opacification.
The North American Children study\textsuperscript{12} found a mortality rate of 30%, with 50% of patients experiencing on-going morbidity. It has become clear that some ILD entities are associated with very high mortality, whereas others have a favorable outcome.

References


\textsuperscript{a} Hospital Materno Infantil de Málaga, Spain

\textsuperscript{b} Facultad de Medicina de Málaga, Hospital Materno Infantil de Málaga, Spain

\textsuperscript{c} Corresponding author.

E-mail address: mcarmen.lopez123@gmail.com

(M.C. López Castillo).

1579–2129/
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Tuberculosis and Microscopic Polyangiitis. A Rare Combination\textsuperscript{y}

\textit{Tuberculosis y poliangitis microscópica. Una asociación muy poco frecuente}

To the Editor:

Tuberculosis (TB) is one of the most common causes worldwide of morbidity and mortality due to infection, with a recorded incidence in Spain in 2015 of 21.5 cases/100,000 inhabitants.\textsuperscript{1}

Vasculitis is a general term for a heterogeneous group of diseases characterized by inflammation and destruction of blood vessel walls.\textsuperscript{2} Most cases are primary, but vasculitis can also be secondary to other diseases, including infections.\textsuperscript{3} At times the difference between TB and vasculitis can be difficult to determine, because they share similar characteristics, and moreover, both entities can coexist in the same patient.\textsuperscript{4} The definitions of vasculitis and its different forms are well established.\textsuperscript{5} We report the case of a patient that presented simultaneous TB and microscopic polyangiitis (MPA).

This was a 68-year-old man with a history of TB, who attended the emergency room with a 1-month history of fever, bloody sputum, asthenia, weight loss, and dyspnea. His temperature was 38.4 ºC, with no other significant findings. Blood tests were normal, and chest X-ray revealed scarring in the upper right lobe and a solid, spiculated parenchymal lesion. Chest computed tomography (CT) showed no changes in the middle and lower fields (Fig. 1A).

No upper respiratory tract involvement was observed. Polymerase chain reaction was positive for \textit{Mycobacterium tuberculosis} in bronchial aspirate and bronchoalveolar lavage. Core needle biopsy of the spiculated lesion revealed necrotizing granulomatous inflammation with multinucleated Langhans giant cells (Fig. 1B), and positive Ziehl–Neelsen staining and polymerase chain reaction for \textit{M. tuberculosis}. The patient developed sudden onset hemoptysis with anemia (hemoglobin>6.8 g/dl, hematocrit 20.8%), acute renal failure (urea 123 mg/dl, creatinine 8.3 mg/dl), oligoanuria and elevated transaminases (values 5 times the upper limit of normal), Intubation, mechanical ventilation, and hemodialysis were required. In view of the patient’s hepatic and renal insufficiency, antituberculosis treatment began with ethambutol, levofloxacin, and streptomycin. Chest CT showed diffusely increased pulmonary radiodensity, mainly ground glass opacities and areas of consolidation in the peribronchovascular region, with moderate left loculated pleural effusion, with a fissural component, that was interpreted as diffuse alveolar hemorrhage (Fig. 1C). Renal biopsy revealed vasculitis with fibrinoid necrosis of the small arteries associated with focal and segmental necrotizing glomerulonephritis with an absence of immunoglobulin, complement and light chain deposits, suggestive of MPA (Fig. 1D and E). Pleural fluid was a lymphocytic exudate; ADA 45 U/L, with no other significant changes. Anti-neutrophil cytoplasmic antibodies (ANCA) (Fig. 1D) were negative. 

The association between TB and vasculitis has been described, but generally always in association with granulomatosis with polyangiitis.\textsuperscript{6,7} As far as we know, this is the second case in which TB has been associated with MPA.\textsuperscript{8} Both diagnoses appear to be confirmed: positive polymerase chain reaction in 2 different samples in the case of TB; and for MPA, granulomatous inflammation with necrosis and multinucleated giant cells in lung tissue

\textsuperscript{y} Please cite this article as: Rivero V, Ricoj Y, Toubes ME, Valdés L. Tuberculosis y poliangitis microscópica: Una asociación muy poco frecuente. Arch Bronconeumol. 2018;54:635–637.