Respiratory Distress, Congenital Hypothyroidism and Hypotonia in a Newborn

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A male infant was born at term and eutrophic at birth. On day 6, he developed severe respiratory distress that required non-invasive ventilation support and oxygen therapy. Clinical examination revealed axial hypotonia, congenital myxoedema, cutaneous jaundice, large fontanelles, and mild macroglossia. The diagnosis of hypothyroidism was confirmed by the neonatal systematic screening results, with an absence of thyroid tissue. Chest high-resolution computed tomography (HRCT) showed diffuse alveolar and interstitial opacities (fig. 1a).

The child was supplemented with L-thyroxine. Non-invasive ventilation could be stopped after a few days, but he remained hypoxic with 73 mm Hg PaO₂ under 1 litre/min oxygen supplementation. At the age of 3 months, oral long-term azithromycin was started followed by intravenous monthly corticosteroid pulses (300 mg/m²/day for 3 days) and oral corticosteroids [1]. At the age of 10 months, his clinical evaluation was stable. A HRCT scan showed a diffuse increase in the ground-glass attenuations. Oral hydroxychloroquine was added but had to be stopped after 4 months because of neutropenia. Progressively, under corticosteroid pulses and azithromycin, his respiratory status improved, and at the age of 2 years, oxygen therapy was discontinued. Neurological evaluation

documented an important motor and speech delay with hypotonia and choreic movements.

The patient's mother, aged 26 years, reported a medical history of abnormal movements since the age of 5 years and chronic cough during childhood, with no proven aetiology. Her clinical evaluation documented benign hereditary chorea appearing in infancy, which had improved up to early adulthood and evolved to myoclonus. She presented compensated hypothyroidism.

Surprisingly, despite the absence of complaints, respiratory investigations revealed stage II NYHA dyspnoea, hypoxemia with 57 mm Hg PaO₂, and a severe restrictive pattern with diffusion impairment on lung function tests. A HRCT scan showed diffuse ground-glass attenuations, sub-pleural cysts and mild lung fibrosis (fig. 1b). A left to right spontaneous massive shunt through the patent foramen ovale was discovered. After percutaneous closure, her respiratory condition improved partially. She was put under azithromycin treatment for 3 months, then continuous oral corticosteroid for only 1 month without any objective improvement. The treatment was recently replaced by hydroxychloroquine.

What is your diagnosis?

Fig. 1. HRCT scan of the two related patients. **a** Chest HRCT scan of the infant (individual III.2, fig. 2) at the age of 16 months showing diffuse ground-glass attenuations. **b** Chest HRCT scan of the mother (individual II.3, fig. 2) at the age of 27 years showing a fibrosing interstitial pattern with bilateral septal thickening and mild ground-glass attenuations.

Diagnosis: Familial 'Brain-Lung-Thyroid Syndrome' Related to a *NKX2-1* Mutation

Surfactant protein disorders were suspected and analysis of the NK2 homeobox 1 gene (*NKX2-1*, OMIM610978), also known as thyroid transcription factor 1 (*TTF1*), revealed the presence of a novel splicing mutation: c.373+2T>C, NM_003317.3. Following the identification of the *NKX2-1* mutation in the baby, a familial screening was proposed, which led to the identification of the *NKX2-1* c.373+2T>C novel mutation in the mother (fig. 2).

NKX2-1 (NM_003317.3) heterozygous mutations have been associated with 'brain-lung-thyroid syndrome' with variable degrees of interstitial lung disease (ILD), thyroid dysfunction (hypothyroidism) and neurological abnormalities (hypotonia and benign chorea) [2–7].

This family illustrates well the large phenotype variability of the disease. Whereas the lung disease started early in life and was severe in the child, the mother presented moderate childhood respiratory disease and evolved towards lung fibrosis in adulthood. The benign chorea was predominant in her and appeared later than usually described, with compensated hypothyroidism [6, 8, 9]. Depending on the series, complete brain, lung and thyroid disease is described in 30–50% of patients with *NKX2-1* mutation [5, 8, 10]. Isolated benign chorea or lung involvement have also been described in 13–24% of cases [4, 5, 8, 10]. The reason why patients display such heterogeneous phenotypes for the same *NKX2-1* mutation is unclear. Various types of molecular defects have been described without phenotype correlations, except for whole-gene deletion that may be associated, unexpectedly, with milder pulmonary disease [4].

In France, systematic neonatal screening for hypothyroidism can lead to the early diagnosis of 'brain-lung-thyroid syndrome'. However, considering the high frequency of incomplete forms of the disease, even in the absence of hypothyroidism, unexplained ILD in a young patient should justify a *NKX2-1* analysis [5].

Corticosteroids are the mainstay of the ILD treatment in children with various surfactant disorders, including *NKX2-1* mutations. Other medications have been used, such as azithromycin for its immunomodulatory properties or immunosuppressive drugs, including hydroxychloroquine [1, 11].

Familial cases of 'brain-lung-thyroid syndrome' are rare, with highly heterogeneous phenotypes, even in a single family. As clinical manifestations can appear over time, an isolated organ disease may not exclude the diagnosis. Therefore, a multidisciplinary management with lung physicians, endocrinologists and neurologists is recommended to propose an early treatment.

Fig. 2. Pedigree of the described family. The index case III.2 (arrow) was diagnosed with 'brain-lung-thyroid syndrome' (black symbol). A heterozygous (+/-) novel splicing *NKX2-1* (NM_003317.3) mutation c.373+2T>C was identified for him and secondarily for his mother (II.3). Both of the mother's parents (I.1 and I.2) presented neither hypothyroidism nor neurological or respiratory symptoms. Chest CT scans were normal. None of them carried the *NKX2-1* mutation (-/-). The neomutation was thus confirmed in the mother.

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Statement of Ethics

The authors confirm that they obtained written informed permission from the adult patient and from the child's guardian for publication in *Respiration*.

Disclosure Statement

The authors declare that they have no financial or other conflict of interest.

Key Words

NKX2-1 · *TTF1* · Interstitial lung disease · Benign hereditary chorea · Hypothyroidism

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