CASE REPORT

Ladd syndrome: a case report of uncommon respiratory findings

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ABSTRACT

Lacrimo-auriculo-dento-digital (LADD) syndrome is a rare genetic disorder caused by mutations in fibroblast growth factor (FGF) or FGF receptors. Specifically, FGF10 regulates multiple stages of structural lung morphogenesis, cellular differentiation, and response to lung injury. In case of its dysfunction, an abnormal pulmonary development with alveolar disruption can occur. Here we report the clinical case of a patient with LADD syndrome with pulmonary impairment and history of spontaneous pneumothorax.

IMPACT STATEMENT

A single-center experience in the diagnosis and management of respiratory disease in a patient with LADD syndrome, with the aim to review the pathogenic hypotheses and suggest a practical algorithm for standardized clinical management.

INTRODUCTION

LADD syndrome is a rare, autosomal dominant disease secondary to genetic alterations in FGF. Typical findings include hypoplasia and aplasia of salivary and lacrimal glands, digital and dental abnormalities, and hearing loss. Although there are few reports of lung disease in individuals with LADD syndrome, there is some evidence that genetic pathways are involved in lung development, leading to variable defects in lung structure and function.

CASE REPORT

Here we report the clinical case of a boy, born at term after cesarian section because of fetal distress. A single left kidney was discovered before birth, but no other perinatal problems were reported. At birth he was small for gestational age (2660 g) and had regular adaptation to extrauterine life. He grew up on the

KEY WORDS

LADD syndrome; pneumothorax; childhood interstitial lung disease; chest CT; fibroblast growth factor.

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lower centiles for weight and height, with normal neurological development. Several physical features were highlighted over the years: reduced lacrimation, lack of saliva, and abnormalities of the fingers and ears. Despite the strong suspicion of a genetic origin, the genetic test was performed when he was five years old. At that age, he also came for the first time to our outpatient clinic. Respiratory complaints were mainly episodic wheezing associated with atopic substratum (oculorhinitis, eczema, polysensitization to grass and tree pollens, ragweed, house dust mites, dog and cat, and food allergy). Meanwhile, genetic results from NGS (Next Generation Sequencing) identified a mutation in the FGF10 (Fibroblast Growth Factor 10) gene consistent with the diagnosis of LADD syndrome. Inhalation therapy was initiated and modulated (inhaled corticosteroids + long-acting beta-agonists, ICS+LABA) over the years, maintaining good control of respiratory symptoms and lung function. He remained clinically stable until adolescence when he was hospitalized at the age of 15 years old after the sudden onset of thoracic pain and cough. No recent trauma or infection was referred. On physical examination, there was no cardiopulmonary impairment, oxygen saturation was normal with eupnea; on thoracic auscultation, a decrease in normal breath sounds was found in the left upper lung field with no other audible breath sounds. Hence, appropriate investigations and treatment were initiated. Blood chemistry tests showed normal blood count with negative C-reactive protein, the nasal swab was negative for viruses (including SARS-CoV-2), and there were no gas exchange abnormalities on blood gas analysis. Considering his previous clinical history, a chest X-ray was performed, which revealed an apical pneumothorax with a maximum size of 18 mm (**Figure 1**). He was hospitalized for clinical observation, along with antibiotic prophylaxis and bronchodilator. Chest X-ray after 48 hours showed an unchanged size of the pneumothorax, although there was no worsening of the boy's clinical condition. At this point, a more sensitive and specific investigation of the lungs was needed, and a chest CT was organized. Several interstitial anomalies were described, specifically: "*Bilateral reticular pattern alteration of the lung parenchyma at several levels (especially at mantle territories and the ventral segments of both upper lobes); interstitial thickening; pseudocysts in the paramediastinal subpleural and along the ventral territories of the upper lobes (largest identified in the left apical, with a transverse diameter of about 18 mm); aspects of retraction associated with the elements adjacent to the alterations described, particularly on the broncho-vascular structures, in the presence of some bronchiectasis; bilaterally, some nodules of dimensions (<1 cm), as well as a focal filling of the small airways"* (**Figure 2**).

Finally, the left pneumothorax was confirmed as unchanged with a thickness of up to 20 mm in the apical area and 23 mm in the antero-basal area. Based on CT findings, the lung abnormalities oriented toward a "childhood interstitial lung disease" (chILD). According to the diagnostic flowchart established by Bush *et al*. (1), specific blood tests (genetic tests for Cystic Fibrosis (CF), surfactant deficiency, and alpha-1-antitrypsin) were performed, with negative results. The boy's stable condition allowed for invasive investigations such as bronchoscopy lung biopsy avoided, and a wait-and-see policy was followed. Lung ultrasound monitored a progressive reduction of the pneumothorax field with total regression on chest radiography performed after one month. The patient was discharged from the hospital and presented to our outpatient clinic for clinical follow-up after one week, with complete resolution of respiratory signs and symptoms. Home therapy was based on inhaled corticosteroids (fluticasone propio-

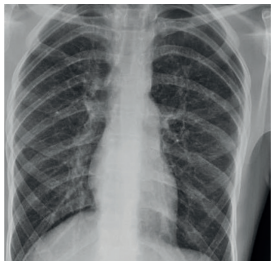

Figure 1. *Left apical pneumothorax.*

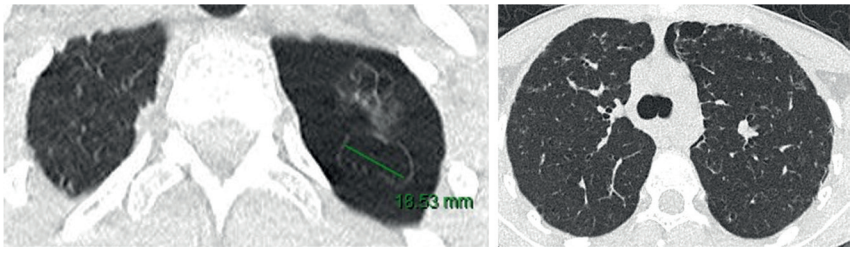

Figure 2. *HRCT showing pseudocysts (on the left image) and reticular pattern with bronchiectasis and nodules (on the right image).*

nate) and long-acting beta-agonists (formoterol) twice daily, as well as avoidance of exercise and air travel because of pneumothorax. Recently, the patient resumed regular physical activity and no longer complained of other respiratory symptoms. Genetic workup was completed with the exclusion of inherited or de-novo defects associated with congenital collagenopathies or folliculin dysfunction.

DISCUSSION

LADD syndrome, also known as lacrimo-auriculo-radio-dental syndrome (LARD) or Levy-Hollister syndrome, is a rare condition secondary to haploinsufficiency of FGF, particularly FGF10, FGF receptor (FGFR)2 and FGFR3 (2). In addition to some typical features involving the salivary and lacrimal glands, ears, teeth, and fingers (**Table 1**), several pulmonary conditions have also been reported anecdotally in individuals with LADD syndrome (3-5), possibly due precisely to FGF10 dysfunction. Indeed, FGF10 has been shown to be a key regulator of lung structure and function in both mouse and human models. Its pleiotropic functions range from morphogenesis of airway branching in utero to proliferation and differentiation of postnatal lung cells, including epithelial-mesenchymal crosstalk (6) and recovery of lung injury after various noxious stimuli (7) (**Figure 3**).
As a result, individuals with LADD syndrome could be affected by a highly heterogeneous spectrum of pneumopathies, from lethal congenital conditions to mild predispositions to chronic lung disease, manifesting after years of environmental “threats” and breathing. Although most of the evidence comes from animal models, in situ hybridization and RNA sequencing techniques in human fetal lung cells have confirmed stable expression of FGF10 during the later stages of human lung development (8), especially during the pseudo glandular and canalicular phase. As a result, many recent works have hypothesized a role of FGF10 signaling alterations in human lung pathologies, such as sudden infant death syndrome (SIDS), early-onset severe interstitial lung disease, bronchopulmonary dysplasia (BPD), lethal lung developmental disorders (LLDD), interstitial pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD) (9, 10). Recently, an intriguing role has been proposed for some specific modifier genes in regulatory loci, which may epistatically interfere with FGF10 phenotypic expression, triggering or amplifying lung diseases (11). In this regard, Karolak *et al*. recently demonstrated the presence of heterozygous copy-number variant deletions or single-nucleotide variants (SNVs) involving TBX4 or FGF10 in children with pulmonary hypoplasias. Most of them had pulmonary acinar dysplasia (PAD), a rare congenital lung malformation secondary to arrested lung development at the pseudo-glandular stage, in which the presence of a few narrower bronchioles without alveoli leads to early and fatal respiratory failure (11). In this paper, they highlighted the central role of TBX4-FGF10-FGFR2 epithelial-mesenchymal signaling in human lung organogenesis and the potentially lethal effects on lung growth in case of genetic anomalies. Growing awareness of the importance of noncoding variants in developmental lung defects has led some authors to propose diagnostic algorithms that include whole genome sequencing (WGS) to address severe respiratory distress in the early-onset infant, especially if it is progressive and refractory (5). Over the years, this could lead to targeting FGF10 to prevent and treat such severe re-

Table 1. *Clinical key features of LADD syndrome, with related signs and symptoms.*

Hypo/aplasia of parotid and salivary glands	Poor salivary flow, xerostomia, dental caries, absence of Stensen duct
Hypo/aplasia of lacrimal glands and lacrimal duct agenesis	Epiphora, recurrent ocular infections, xeropthalmia, nasolacrimal obstruction, dacryocystocele
Dental anomalies	Microdontia, hypodontia, enamel dysplasia, peg-shaped incisors
Digital anomalies	Hypoplastic, accessory or triphalangeal thumb, clinodactyly, syndactyly
Ear anomalies	Low-set ears, cryptotia, cupped auricles, cochlear hypoplasia, incus and stapes anomalies, hearing loss
Kidney anomalies (rare)	Unilateral renal agenesis
Oral cavity anomalies (rare)	Bifid uvula, bald tongue

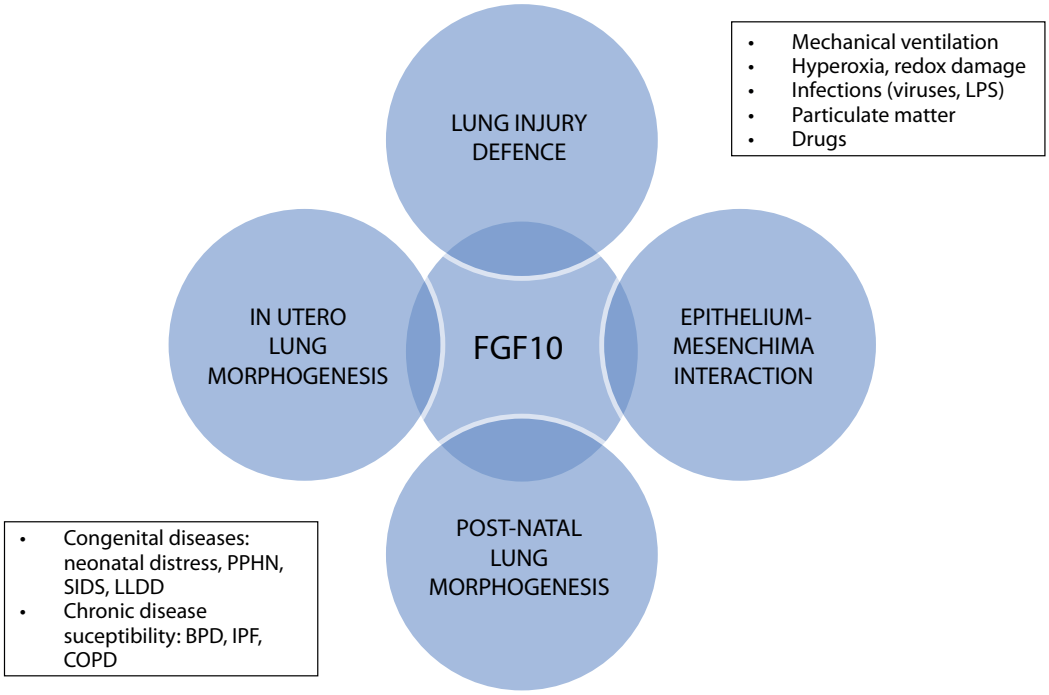

Figure 3. *Role of FGF10 signaling in pulmonary physiology and pathology.*
Redox: oxydative-reductive; LPS: lipopolysaccharides; PPHN: persistent pulmonary hypertension of the newborn; SIDS: sudden infant death syndrome; LLDD: lethal lung developmental disorders; BPD: bronchopulmonary dysplasia; IPF: interstitial pulmonary fibrosis; COPD: chronic obstructive pulmonary disease.

spiratory diseases. However, there are still preclinical concerns about its long-term tumorigenic potential and some evidence of cystic adenomatoid malformations (12) in mouse models overexpressing FGF10. To our knowledge, this is the first report of spontaneous pneumothorax in a child with LADD syndrome. Furthermore, no other cases of emphysematous interstitial lung disease in human children with LADD have been reported. However, De Langhe *et al*. described a similar "emphysema-like" pattern in mouse lungs as a consequence of premature arrest of terminal airway development (13). Whether the pneumothorax depends directly on FGF10 defects or is simply accidental needs further investigation. In any case, emphysematous interstitial areas resulting from altered alveolarization may predispose these subjects to recurrent episodes of pneumothorax and pneumomediastinum. Because of its rarity, specific guidelines for managing LADD syndrome are still lacking. However, the pulmonary disease can seriously impact the health and quality of life of these individuals throughout their lives. In light of this, we suggest a comprehensive 10-step pulmonary workup in the management of individuals with LADD disease:

1. At the first physical examination, perform a complete blood count, biochemistry, c-reactive protein, and capillary blood gases.
2. Test for immunoglobulins, immunoglobulin G (IgG) subclasses, and serum alpha1-antitrypsin, especially in cases of recurrent respiratory infections. Schedule a sweat test and first-line genetic testing for cystic fibrosis transmembrane conductance regulator (CFTR) mutations.
3. Assess lung structure and function with two-projection chest radiography and spirometry with bronchodilator response testing. Perform plethysmography if indicated and DLCO.
4. High-resolution chest CT should be scheduled based on the results of spirometry or chest radiography or in the presence of persistent respiratory symptoms.
5. If there are signs and symptoms of pulmonary hypertension or exertional dyspnea, a complete cardiologic evaluation and possibly an exercise test should be arranged.
6. Reassess the patient clinically twice a year and repeat pulmonary function tests at least once a year.

7. Recommend all vaccinations, especially the annual flu vaccine, and suggest strict avoidance of active and passive smoking, including e-cigarette smoking.
8. If susceptibility to pneumothorax is proven over time, avoid strenuous exercise, contact sports, and diving.
9. Institute respiratory physiotherapy programs and aggressive early treatment of respiratory infections. Assess the need for antibiotic prophylaxis.
10. Share management decisions with geneticists, otolaryngologists, ophthalmologists, dentists, and nephrologists. Suggest genetic counseling before pregnancy and early screening in utero for LLDD.

In conclusion, in this particular clinical case, lung disease could be a manifestation of LADD syndrome or a chance finding. Analyzing the chILD classification system, there is an "unknown" category for cases undiagnosed by biopsy, with inconclusive diagnosis, or with some missing information. Severe lung disease with features of LADD syndrome could represent a distinct syndrome belonging to the chILD group with a yet undetermined genetic etiology. NGS will allow us to discover new entities and better classify childhood disorders. Further studies are needed to define the involvement of pulmonary and bronchial structures in children with LADD syndrome to guide appropriate therapy and management.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Authorship

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Author contributions

GR: conceptualization, writing - original draft. BA: conceptualization, writing - original draft. MDF: writing, review and editing. MV: writing, review and editing. AL: conceptualization, formal analysis, and supervision. GLM: supervision.

Ethical approval

Human studies and subjects

The Authors confirm that the patient has provided his consent to the anonymous publication of clinical information.

Animal studies

N/A.

Data sharing and data accessibility

N/A.

Publications ethics

Plagiarism

Any overlaps with other articles are appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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