

## LACHT association with hypoplasia of the upper airway. Clinical case

### Asociación LACHT con hipoplasia de la vía aérea superior. Caso clínico

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### Abstract

**Introduction:** The Mardini-Nyhan or LACHT association is a clinical condition of low prevalence that presents with pulmonary, cardiac and limb abnormalities, in which genetic etiology is not clearly documented to date. **Objective:** To describe the case of a 4-month-old child and the literature review of cases reported on this association, with the purpose of exposing the alterations found and thus guide the early diagnosis of this entity. **Clinical case:** 4 months old girl, who admitted to intensive care in mixed respiratory failure, with pulmonary, cardiac and limb disorders that meet criteria for LACHT association, additionally documents hypoplasia of the upper airway, which worsens the evolution, increases the difficulty in mechanical ventilation and favors the fatal outcome at 7 days of hospitalization. **Conclusions:** LACHT association is a rare pathology in which the clinical findings make it possible to suspect the diagnosis, this is the first case diagnosed in the Americas and the number 11 case in the world literature and brings as a new finding the association with hypoplasia of the upper airway.

### Keywords:

Mardini-Nyhan association,  
LACHT association,  
lung agenesis

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## Introduction

Mardini-Nyhan association or LACHT syndrome (*Lung agenesis, congenital heart defects and thumb anomalies*) is a clinical condition characterized by pulmonary agenesis that may be unilateral or bilateral, with congenital heart defects and thumb abnormalities<sup>1-3</sup>. The first description of this association was made by Mardini and Nyhan in 1985<sup>1,2,4,5</sup>, where they studied four patients with pulmonary agenesis, two of them had right partial pulmonary agenesis and two of them had left pulmonary agenesis, 3 of them were female<sup>5</sup>. Consanguinity seems to be related to this association since in the first description of four patients, all of them were the product of consanguineous parents<sup>1</sup>. However, in cases published subsequently, no consanguinity or chromosomal alterations have been described, so the etiology remains unclear<sup>1,2,4,6</sup>. Up to now, 10 cases have been documented of this pathology<sup>1,3</sup>; considering that no confirmatory tests exist, we present case number 11, which fulfills the clinical findings described in this clinical condition.

## Clinical case

Four-month-old child that, 10 days before admission to children's hospital, had watery stools without mucus or blood which improved with symptomatic treatment; subsequently she had hacking cough neither cyanotic nor emetic, respiratory distress and fever. Notion of positive contagion: older sister and father with upper respiratory infection. The child is hospitalized with laryngotracheobronchitis diagnosis, she is treated with systemic and inhaled corticosteroid, nebulized adrenaline, oxygen by high flow system, and hydration, without improvement. Paraclinical tests performed at admission suggest a bacterial infection, therefore, antibiotic treatment with ampicillin sulbactam started. Tests for respiratory syncytial virus, influenza, adenovirus and parainfluenza were negative. The patient has a torpid evolution, she requires transfer to the pediatric intensive care unit (PICU) and begins mechanical ventilation.

Case history: Second daughter of non-consanguineous parents; mother is 24 years old and father is 28 years old. 36 weeks cesarean section delivery due to oligoamnios, prenatal diagnosis of pulmonary agenesis and dextrocardia detected in the 20<sup>th</sup> week of gestation by detailed ultrasound; weight 2,800 g (6.17 lbs) and length 46 cm (18.11 in). She required hospitalization in neonatal unit for 20 days and mechanical ventilation for 2 days. No further hospitalizations. The child is oxygen-dependant via low-flow nasal cannula; she has a mild delay in psychomotor development. Nega-

tive family history. Sister is 2 years and 6 months old and healthy.

In the interdisciplinary ambulatory clinical follow-up by pediatrics, pediatric cardiologist, pediatric pulmonologist, and geneticist, clinical evaluations and complementary studies were performed making the following findings:

- Chest CT angiography with three-dimensional reconstruction reports absence of right pulmonary artery and right main bronchus. The heart and mediastinum are located in the right hemithorax, diameter of main trunk of pulmonary artery greater than 9.2 mm, there was no intraluminal defects in the pulmonary arteries, no left-to-right shunt, general size increase of the right cavities, compensatory hyperinflation of the left lung (Figure 1).
- Two-dimensional and color M-mode Doppler echocardiography: moderate pulmonary hypertension, dextrocardia with dextroapex, good biventricular function, normal coronary arteries, normal foramen ovale for the age.
- 46, xx karyotype.
- FISH result for 22q11 microdeletion was negative. No other cytogenetics tests were performed.
- Positive clinical findings: wide forehead, decreased vesicular breath sound in right hemithorax, grade III/VI heart murmur in all focuses, hypoplastic right thumb with proximal insertion.

The diagnosis of LACHT syndrome is made by the findings of right pulmonary agenesis, absence of pulmonary artery, dextrocardia with dextroapex, pulmonary hypertension and thumb abnormalities.

During the stay in PICU, clinical evolution of the child is torpid with poor response to management to non-invasive ventilation, requiring advanced airway



**Figure 1.** Thorax computed angiotomography with tridimensional reconstruction: Absence of right pulmonary artery and right bronchus, the heart and mediastinum are localized on the right side hemithorax, no intraluminal defects in pulmonary arteries, global increase in right cavities

management (difficult airway, tracheal tube did not go through the cricoid ring). She remains under conventional mechanical ventilation with single lung protective strategy (permissive hypercapnia and controlled hypoxemia), chest x-ray with loss of radiolucency of right hemithorax and compensatory hyperinflation of the left lung (Figures 2 and 3). The patient developed septic shock requiring vasoactive support with noradrenaline and milrinone. Two-dimensional and color M-mode Doppler echocardiography with the same previous findings, sildenafil was indicated for pulmonary hypertension. The patient presents a cardiopulmonary arrest that responds to advanced resuscitation procedures after 4 minutes. Follow-up by cardiology is considered appropriate management for pulmonary hypertension (PHT). The child presents severe oxygenation disorder, it is decided to change to high-frequency ventilation; hemodynamic and respiratory goals are not achieved; therefore, the patient is brought back to conventional ventilation. Patient required greater vasoactive support, due to septic shock and catecholamines resistance, vasopressin and hydrocortisone were added. Given the clinical evolution and the difficulties in mechanical ventilation, bronchofiberscopy was carried out, showing hypoplasia and a decreased airway diameter in all its extension from the vocal cords to the beginning of the segmental bronchi of the left lung, there was no ostium for the main bronchus of the right lung. It was considered that she was not a candidate for surgical management.

There was no renal, hematologic or gastrointestinal dysfunction while the patient was in PICU. She received enteral nutrition with full feeds and appropriate tolerance. From a metabolic point of view, she had moderate hypokalemia, which was corrected intravenously; she had no seizures or abnormal movements, and achieved adequate sedation and analgesia with opioids and ketamine.

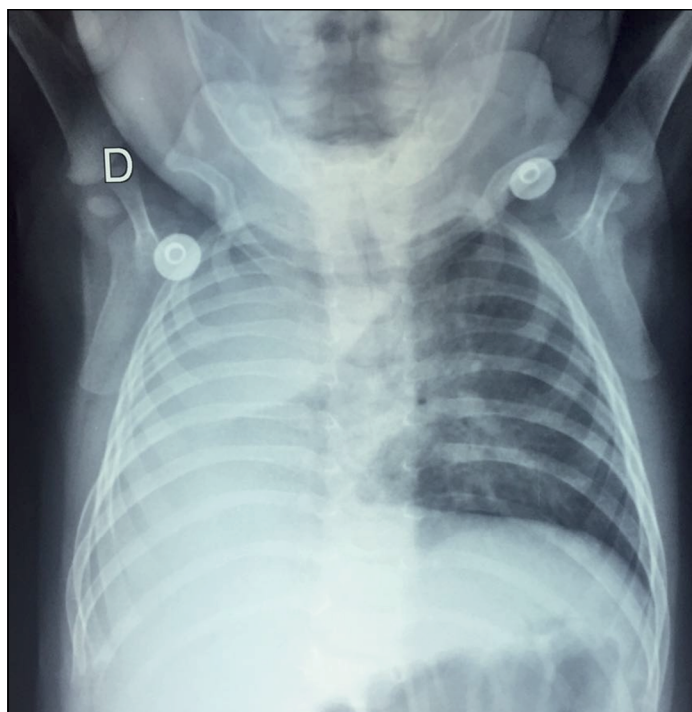
The deterioration of radiologic outcomes and oxygenation index revealed a worsening evolution of the patient, leading to acute respiratory distress syndrome (ARDS). The child required an increase in vasoactive support, but without improvement of the microcirculation and macrohemodynamics, possible due to severe respiratory acidemia. The patient experienced cardiopulmonary arrest with no response to resuscitation procedures; she dies 7 days after admission to the institution.

## Discussion

The LACHT association is a clinical condition characterized by uni or bilateral pulmonary agenesis, congenital heart defects and thumb anomalies in which



**Figure 2.** Chest X ray with loss of radiolucency of the right hemithorax related to pulmonary agenesis, compensatory hyperinsufflation of the left lung, central venous catheter, orotracheal tube and gastric tube in right position.



**Figure 3.** Chest X ray with loss of radiolucency of the right hemithorax related to pulmonary agenesis, compensatory hyperinsufflation of the left lung, alveolar opacities on the base of left lung.

the cause is not clearly documented<sup>1-3</sup>. During the study of pulmonary agenesis, the initial description of the patients was carried out.

Pulmonary agenesis was first described by Pozze in 1673 in the necropsy of a female patient<sup>6-10</sup>. It is an uncommon defect<sup>10-12</sup>, with a reported prevalence

of 0.5 to 1 per 100,000 births and 1 in 10,000-15,000 necropsies. This condition is characterized by the absence of bronchi, parenchyma and pulmonary vasculature<sup>2,7,10,13,14</sup>. It can be unilateral or bilateral<sup>7,15</sup>, where the first one is the most frequent. Right agenesis is associated with greater complications<sup>7</sup> such as cardiovascular (14%), muscular-skeletal (12%), gastrointestinal (14%), genitourinary (9%), and vascular defects (9%). It can appear as an individual symptom or as a clinical symptom of other diseases, such as Goldenhar syndrome, VACTER association, 22q11 microdeletion syndrome, Holt-Oram syndrome and Opitz-G syndrome.

Alteration in embryologic development occurs in the fourth week of gestation, caused by an unequal division of the two respiratory diverticulum<sup>7,10,12,14</sup>, the triggering factor is not clear but some options might be: genetic factors, vitamin A deficiency, folic acid deficiency, viral infections, and salicylates exposure<sup>7,8,12,13</sup>.

In cases of unilateral pulmonary agenesis, life expectancy depends on the associated comorbidities<sup>6,10,16</sup>. Cases of bilateral pulmonary agenesis are deadly; such as the first one described by Morgani in 1955<sup>17</sup>. One of the reported bilateral pulmonary agenesis cases was a 29-week preterm patient with prenatal ultrasound within the normal range, who was born without respiratory effort and failed endotracheal intubation associated with difficult airway. The patient died 26 minutes after; necropsy revealed bilateral pulmonary agenesis with obstructed 1-cm diameter trachea at the end, a lethal condition<sup>15</sup>.

Pulmonary agenesis was initially classified based on the groups described by Schneider and Schwalbe, they are group 1: total absence of lung and pulmonary artery; group 2: lung and pulmonary artery absence with rudimentary bronchus from the trachea; and group 3: hypoplastic lung with a well-formed bronchus<sup>5</sup>. Subsequently, this classification was modified by Boyden in 1955 as follows type 1 (agenesis): total absence of bronchi and lung without vascular supply on the affected side; type 2 (aplasia) rudimentary bronchus and complete absence of pulmonary parenchyma; and type 3 (hypoplasia): presence of variable amount of bronchial tree, pulmonary parenchyma and vascular supply<sup>7,10-12</sup>. The patient abovementioned was classified as type 1 (agenesis).

The reported case presented by Jaiman et al. is the only case of stillbirth born to a 29-years-old mother, with normal prenatal check-ups until the 32<sup>nd</sup> week of gestation when they show truncus arteriosus type I and intrauterine growth restriction. At week 36 there was no cardiac activity, therefore, they induced labor delivering a female stillborn, weight 2.6 lbs (1,200 gr), which had clinical findings of LACHT syndrome (rudimentary first phalanx and oblique first metacarpal, right pulmonary agenesis, ipsilateral pulmonary artery

absence, hypoplastic left heart, patent foramen ovale, interventricular communication, and coronary sinus drainage from left superior vena cava)<sup>2</sup>.

Prenatal diagnosis is a great instrument for detecting heart and lung genetic alterations, as did in the present case in which at the 20th week of gestation by means of detailed prenatal ultrasound, pulmonary agenesis and cardiac alterations were documented, as in the case of the patients reported by Hastings et al.<sup>4</sup>. Findings detected in the prenatal period alert possible complications in the neonatal stage and can help to provide the interdisciplinary treatments these patients need.

In one of the patients reported by Hastings et al., it was documented that the older brother had complex congenital heart disease, bilateral alteration of pulmonary segmentation without limb abnormality<sup>4</sup>.

The clinical presentation of patients with pulmonary agenesis and those patients with LACHT syndrome is widely varied, some of them present symptoms from birth while others reach adolescence and adulthood without presenting symptoms or being diagnosed. In the first 5 years of life, many of these patients have recurrent sibilant rhonchi or lung infections and approximately 50% of them die at this age. Our patient died at 4 months of age<sup>4,8,10,12,16,17</sup>.

To this date, patients reported with LACHT syndrome have the following characteristics: 91% of cases were female, only one of the 11 patients had family history fulfilling pulmonary and cardiac criteria but without thumb alterations. In 63.6% of cases, pulmonary agenesis was right sided. Some of the main documented cardiac abnormalities are: atrial septal defect, ventricular septal defect, total anomalous pulmonary venous drainage, hypoplastic aortic arch, pulmonary stenosis, left superior vena cava, and dextrocardia with dextroapex. In thumb anomalies there have been reports of duplication, triphalangeal thumb, hypoplastic thumb with proximal insertion, and rudimentary thumb. In none of the reported cases alterations in the karyotype, in the fluorescence in situ hybridization test or in molecular studies have been documented<sup>3</sup>.

Our patient has the peculiarity of an alteration in the morphology of the upper airway that had not been documented in other cases. In this case hypoplasia and a diameter decrease in the airway was documented in all its extension from the vocal cords to the beginning of the left lung segmental bronchi, without ostium for the right lung main bronchus, which is a finding that represented an additional risk factor for the treatment of infectious respiratory disease and a decrease in therapeutic options, such as tracheostomy.

Among the complications of these patients and complications faced by health professionals in both the emergency room and the PICU, decompensated



heart failure and respiratory tract infections are included. Patients with a reported cause of death in the literature reviewed and including the current case are: a 1-month-old patient who dies of multi organ dysfunction secondary to Salmonella sepsis and three patients who died of pulmonary sepsis at four, nine and fifteen months of age without bacterial isolation<sup>3</sup>.

## Conclusions

The association Mardini-Nyhan or LACHT syndrome is a clinical condition of low prevalence, characterized by pulmonary agenesis, congenital heart defects and thumb anomalies, where the cause is not clearly defined, there are no genetic mutations or chromosomal alterations documented to date. It is important to know the clinical findings of this association in order to identify patients early, perform complementary studies looking for other associated alterations, establish the necessary supportive treatment and nourish the current literature on this topic.

## 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.

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## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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