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Neuroendocrine Cell Hyperplasia of Infancy: an underrecognized disorder. Case report

Hiperplasia de células neuroendocrinas de la infancia: un trastorno poco reconocido. Reporte de un caso

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ABSTRACT. Neuroendocrine cell hyperplasia of infancy is a type of interstitial and diffuse lung disease in children. We present the clinical case of a male infant, who began showing symptoms at three months of age characterized by poor weight gain, tachypnea and wheezing; history of a hospitalization with diagnosis of bronchiolitis, but did not show clinical improvement despite treatment with systemic glucocorticoids and bronchodilators. A study approach was initiated with chest tomography, revealing ground-glass opacities primarily affecting segment 3 of the right lung, as well as the middle lobe and lingular region, concluding diagnosis of childhood neuroendocrine cell hyperplasia based on the clinical and tomographic findings. Interstitial lung disease in infants is often underrecognized, as its symptoms can easily be mistaken for other acute lung pathologies. Therefore, it is important to maintain a high index of suspicion to enable timely diagnosis.

Keywords: neuroendocrine cell hyperplasia, childhood interstitial lung disease, tachypnea.

RESUMEN. La hiperplasia de células neuroendocrinas de la infancia es una forma de enfermedad pulmonar intersticial y difusa infantil. Presentamos el caso clínico de un lactante masculino que inició sus síntomas a los tres meses de edad caracterizado por pobre ganancia pondoestatural, taquipnea y sibilancias con antecedente de una hospitalización con diagnóstico de bronquiolitis, sin presentar mejoría clínica a pesar de tratamiento con glucocorticoides sistémicos y broncodilatadores. Se inició abordaje de estudio con tomografía de tórax que evidenció vidrio deslustrado que afecta principalmente segmento 3 de pulmón derecho, así como lóbulo medio y región lingular, concluyendo diagnóstico de hiperplasia de células neuroendocrinas de la infancia con base a la clínica y los hallazgos tomográficos. La enfermedad pulmonar intersticial en lactantes es poco reconocida, ya que sus síntomas suelen confundirse fácilmente con otras patologías pulmonares agudas. Por lo tanto, es fundamental mantener un alto índice de sospecha para poder realizar diagnósticos oportunos.

Palabras clave: hiperplasia de células neuroendocrinas, enfermedad pulmonar intersticial infantil, taquipnea.

Abbreviations:

chILD = Childhood Interstitial Lung Disease.
chILDRN = Children's Interstitial and Diffuse Lung Disease Research Network.
NEHI = Neuroendocrine Cell Hyperplasia of Infancy.

INTRODUCTION

Neuroendocrine cells hyperplasia of infancy (NEHI), formerly known as persistent childhood tachypnoea, is a type of childhood interstitial lung disease (chILD). This condition is characterized by clinical signs and specific

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tomographic findings. ChILD refers to a disorder that affects the lung interstitium and distal airways, resulting in an abnormal gas exchange. These pathologies are difficult to diagnose; and children with chILD often have tachypnoea, hypoxia and crackling respiratory sounds.[1-3]

The classification scheme proposed by Children's Interstitial and Diffuse Lung Disease Research Network (chILDRN) is organized into two categories: «Specific interstitial lung diseases in children» and «Non-specific interstitial lung diseases in children» *(Table 1)*.[1,3,4]

Epidemiological data on childhood neuroendocrine cells hyperplasia are limited and the exact incidence and prevalence of this disease is unknown. However, it is considered a rare condition, probably due to the low recognition of patients with NEHI. The chILDRN established a prospective registry that included the participation of 25 centers in the United States, with a total of 683 patients diagnosed with different childhood lung diseases. Of these, 155 (23%) were diagnosed with NEHI.[5] At Vanderbilt Children's Hospital, 93 chILD cases were retrospectively

Table 1: Childhood interstitial lung disease classification.

Specific interstitial lung diseases in children	Non-specific interstitial lung diseases in children
A. Diffuse developmental disorders	**A. Normal host disease**
1. Acinar dyskinesia 2. Congenital alveolar dysplasia 3. Alveolocapillary dysplasia with poor alignment of the pulmonary veins	1. Infectious and post-infectious processes 2. Environmental agent-related disorders: • Hypersensitivity pneumonia • Toxic inhalation 3. Aspiration syndrome 4. Eosinophilic pneumonia
B. Growth abnormalities	**B. Systematic diseases with pulmonary involvement**
1. Pulmonary hypoplasia 2. Chronic neonatal lung disease: • Bronchopulmonary Dysplasia • Acquired chronic lung disease in term newborn 3. Lung structural changes related to chromosomal abnormalities: • Trisomy 2 • Others 4. Associated with congenital heart disease in chromosomally normal children	1. Immune-related diseases 2. Deposit Diseases 3. Sarcoidosis 4. Langerhans cell histiocytosis 5. Neoplastic infiltrates
C. Specific conditions of undefined etiology	**C. Diseases of the immunocompromised host**
1. Pulmonary interstitial glycogenosis 2. Childhood neuroendocrine cell hyperplasia	1. Opportunistic infections 2. Related to therapeutic intervention 3. Related to transplantation and rejection 4. Diffuse alveolar damage of unknown etiology
D. Disease due to defects in surfactant function	**D. Diseases that mimic interstitial diseases**
1. Surfactant Protein B mutations: dominant histological pattern, pulmonary alveolar proteinosis, and variants 2. Surfactant protein C mutations: dominant histological pattern, chronic pneumonitis of childhood; also desquamative and nonspecific interstitial pneumonia 3. ABCA3 mutations: dominant histological pattern, pulmonary alveolar proteinosis and variants. Also chronic pneumonitis of childhood, desquamative interstitial pneumonia, nonspecific interstitial pneumonia 4. Histology compatible with surfactant defects, but without recognized genetic etiology: • Alveolar pulmonary proteinosis • Chronic pneumonitis of childhood • Desquamative interstitial pneumonitis • Nonspecific interstitial pneumonia	1. Arterial hypertensive vascular disease 2. Congestive vascular disease including veno-occlusive disease 3. Congestive changes related to cardiac dysfunction 4. Lymphatic disorders

Adapted from: Kurland G, Deterding RR, *et al.* American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy.

reviewed between 1994 and 2011, identifying eight cases of NEHI, including five that had not been previously recognized prior to this review.[6]

Deterding et al., conducted a retrospective review of clinical cases, which included 15 children with signs and symptoms of chILD without an identified etiology. Morphometric analysis suggested that these children could constitute a different group of pediatric patients, characterized by the absence of known lung diseases, along with clinical sings and symptoms of chILD and idiopathic neuroendocrine cells hyperplasia of infancy. Clinically, the mean age of onset of symptoms was 3.8 months (range 0 to 11 months) After an average follow up of five years, no deaths were reported and the patients showed improvement.[2]

NEHI's cause is unknown; however, clinical studies have suggested a possible genetic influence, as familial patterns have been observed in some cases and the presence of a heterozygous mutation in the NKX2-1 gene.[7]

A clinical case of NEHI is described focusing on the clinical presentation, the diagnostic process and the importance of early suspicion for timely diagnosis.

CASE PRESENTATION

This is a year and eight months male breastfeeding patient, born at term with a weight of 3,200 g and height of 51 cm. In his hereditary family history stands out a sister with asthma diagnosis. In his pathological personal history there is an evaluation at three months of age by a pediatrician because of poor weight gain, tachypnoea and wheezing, managed with salbutamol aerosol 100 µg every eight hours, with partial improvement; at four months of age he was again assessed because of a picture characterized by wheezing and absence of weight gain, without a treatment modification or establishment of a definitive diagnosis. Hospitalized at five months of age with bronchiolitis diagnosis without taking a respiratory pathogen panel with a normal chest X-Ray, he received hospital treatment with methylprednisolone 2 mg/kg/day, inhaled salbutamol 0.15 mg/kg/day every eight hours and supplemental oxygen one liter per minute, discharged with treatment based on salbutamol with ipratropium bromide aerosol 200 µg/40 mg every eight hours and fluticasone aerosol 100 µg every 12 hours with the use of aerochamber.

Due to the recurrence of the respiratory events, the patient was assessed by the Pediatric Pneumology area without a definitive diagnosis being concluded, he received treatment with fluticasone 100 µg every 12 hour. Despite this, there was no clinical improvement, persisting with poor height-weight gain, hypoxemia and tachypnoea; he was again assessed by Pediatric Pneumology, suspecting interstitial lung disease of the infant, so a chest tomography was performed that showed ground glass that mainly affects segment 3 of the right lung, as well as the middle lobe and lingular region, associated to air trapping data. The patient was assessed by Pediatric Cardiology, which diagnosed pulmonary hypertension and ruled out structural defects. Based on these findings it was decided to begin management with continuous supplemental oxygen at one liter per minute, budesonide/formoterol aerosol 80 µg/4.5 µg two shots every 12 hours, prednisolone 1 mg/kg/day, salbutamol and ipratropium bromide aerosol 200 µg/40 µg every six hours, sildenafil 1.5 mg/kg/day and azithromycin 8 mg/kg/dosis every other day. However, despite the treatment the patient persisted with tachypnoea, wheezing and hypoxemia, so he was referred to our National Medical Center *20 de Noviembre* for a complementary diagnosis. He was assessed by the Pediatric Pneumology Service at one year and two months of age, it was corroborated the presence of hypoxemia of up to 79%, tachycardia and tachypnoea upon removal of supplementary oxygen, in the physical examination with presence of *pectus excavatum* and generalized velcro rales. The approach began ruling out more frequent pathologies such as cystic fibrosis by determining chlorine in sweat, the results were negative (7 y 0 mmol/L), as well as immunodeficiencies with an immunoglobulin profile within the normal limits. Based on the high suspicion of interstitial lung disease of infancy, a chest tomography was performed *(Figure 1)*, which showed air trapping data and ground glass in the middle lobe and lingular region. The echocardiogram showed mild hypoplasia of the transverse aorta, pulmonary systolic pressure 34 mmHg, mean pulmonary pressure 23 mmHg. Based on the clinical data, fulfilling nine points of the NEHI Clinical Score, 3 tomographic findings of butterfly wings and the poor response to systemic steroid treatment, a diagnosis of neuroendocrine cell hyperplasia is concluded.

Within the management, inhaled steroids were initiated at medium doses and a gradual reduction of systemic steroids until their complete suspension, as well as the continuous use of supplemental oxygen at two liters per minute. In the follow-up consultations, daytime suspension of supplemental oxygen was achieved, maintaining saturations of 94-95%. During sleep, supplemental oxygen use by nasal prongs was maintained at 0.25 liters per minute with pulse oximetries of 94-96%. A decrease in dyspnoea events was observed, and no new episodes of wheezing requiring hospital admission have occurred.

DISCUSSION

ChILD manifests itself with symptoms such as tachypnea, crackling, hypoxemia and/or diffuse infiltrates, which should alert the search for more specific interstitial lung disorders. ChILD is difficult to define due to the diversity of diseases

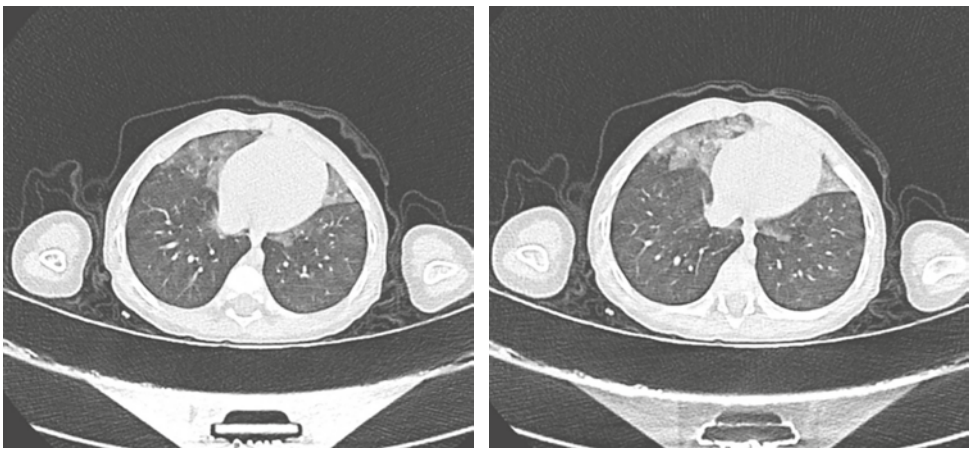

Figure 1:

Simple computed tomography of the chest: ground glass in the middle lobe and lingular region.

it encompasses, forming a large and heterogeneous group, mostly made up of rare disorders. These disorders are associated with considerable morbidity and mortality, presenting significant challenges in both diagnosis and treatment.[8] The American Thoracic Society suggests that, after ruling out common diseases that can cause diffuse lung disease (cysticfibrosis, gastroesophageal reflux and recurrent aspiration, structural airway abnormalities, lung infection, congenital heart disease, congenital or acquired immunodeficiency, primary ciliary dyskinesia), a patient be considered to have «chILD syndrome» if they meet at least three of the following four criteria:[1]

1. Respiratory symptoms (cough, shortness of breath, or exercise intolerance).[1]
2. Respiratory signs (resting tachypnea, auscultation rattles, pulling, acropaquias, growth retardation or respiratory failure).[1]
3. Hypoxemia.[1]
4. Diffuse abnormalities on a chest X-Ray or chest CT scan.[1]

For patients with chILD syndrome it is recommended to perform a series of diagnostic tests to accurately determine the diagnosis of the child. Regarding NEHI, an under-recognized disorder, it is crucial to consider the Clinical Score, which helps identify patients with clinical characteristics compatible with NEHI. This score consists of 10 elements: 1) onset of symptoms before 12 months of age, 2) growth retardation, 3) absence of acropachy, 4) absence of cough in a state of well-being, 5) absence of wheezing in a state of well-being, 6) abnormal chest wall (chest in a barrel or pectus excavatum), 7) crackles, 8) hypoxemia, 9) tachypnoea and 10) retractions. Each element present adds 1 point, and the total score is the sum of these values, with a maximum of 10 points. A score of 7 or higher is considered indicative of NEHI.[3]

Pulmonary function tests in children reveal varying degrees of airflow obstruction. Typical findings on high-resolution computed tomography (HRCT) include ground glass opacities, primarily in the middle lobe, lingula, and/or perihilar regions, along with air trapping showing a mosaic pattern. The diagnosis of INHN can be established clinically by HRCT within an appropriate clinical context. Occasionally a lung biopsy may be necessary, where histopathologic findings of NEHI show an increase in the percentage of neuroendocrine cells in the airways, which can be better identified by bombesin immunostaining.[3,9]

Children with HNHI treated with bronchodilators and glucocorticoids have not experienced improvement in their symptoms, unlike those who might have asthma. Dervaux et al., in a study with a cohort of 54 patients to analyze their long-term evolution, reported that corticosteroids were widely prescribed at the time of diagnosis, but no evident respiratory or nutritional improvement was observed during follow-up. Their results indicate that NEHI shows overall positive, although uneven, improvement over time.[2,10]

In the particular case of our patient, he presented the clinical data to suspect NEHI supported by the main tomographic findings found and no response to systemic steroids, showing clinical improvement over time and only with supportive treatment.

CONCLUSIONS

NEHI is a disease with as yet unknown incidence and prevalence, categorized as a rare disease; however, this could be underestimated due to the low level of recognition of the disease. The diagnosis of NEHI is based on clinical and tomographic findings, highlighting the importance of defining specific clinical characteristics that help physicians in their identification. This would not only facilitate a more accurate diagnosis, but also open new areas for future research, seeking to improve understanding and

management of this under-recognized and potentially under-diagnosed condition.

Conflict of interests: the authors declare no conflict of interests.

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