








Persistent tachypnea of infancy: Follow up at school age

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Abstract

Background: Persistent tachypnea of infancy (PTI) is a rare pediatric lung disease of unknown origin. The diagnosis can be made by clinical presentation and chest high resolution computed tomography after exclusion of other causes. Clinical courses beyond infancy have rarely been assessed.

Methods: Patients included in the Kids Lung Register diagnosed with PTI as infants and now older than 5 years were identified. Initial presentation, extrapulmonary comorbidities, spirometry and clinical outcome were analyzed.

Results: Thirty-five children older than 5 years with PTI diagnosed as infants were analyzed. At the age of 5 years, 74% of the patients were reported as asymptomatic and did not develop new symptoms during the observational period at school-age (mean, 3.9 years; range, 0.3-6.3). At the age of about 10 years, none of the symptomatic children had abnormal oxygen saturation during sleep or exercise anymore.

[Correction added on 19 August 2020, after first online publication: Projekt Deal funding statement has been added.]

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Lung function tests and breathing frequency were within normal values throughout the entire observational period.

Conclusions: PTI is a pulmonary disease that can lead to respiratory insufficiency in infancy. As at school age most of the previously chronically affected children became asymptomatic and did not develop new symptoms. We conclude that the overall clinical course is favorable.

KEYWORDS

children's interstitial lung disease, lung function test, neuroendocrine cell hyperplasia of infancy, pulmonary function test, rare diseases

1 | BACKGROUND

Children's interstitial lung diseases (chILD) cover a heterogenic group of rare pediatric disorders affecting the lung parenchyma, the conducting airways and alveolar spaces. The leading symptoms are tachypnea, hypoxemia, retractions, crackles, and failure to thrive.¹ Only limited data exists on the frequency of chILD. The incidence rate of chILD is suspected to be 0.1 to 16 per 100.000 children per year and prevalence rate 1.3 to 3.6 per million children.²⁻⁵ The current categorization system of chILD lists four groups that are more prevalent among infants than in older children or adults: "Diffuse development disorders of the lungs," "Abnormalities of alveolar growth," "Disorders related to surfactant dysfunction," and "Conditions of undefined etiology."^{2,6} The latter comprises among others "Persistent tachypnea of infancy (PTI)" and "Neuroendocrine cell hyperplasia of infancy (NEHI)."^{2,6,7}

PTI was described in 2001⁸ as the more comprehensive description of "Chronic idiopathic bronchiolitis of infancy" in 1997.⁹ Infants with PTI typically present with tachypnea and hypoxemia in the first months of life. Clinical examination reveals retractions, fine crackles and failure to thrive.^{1,6,8,10,11} Other diseases with similar clinical presentation must be ruled out, especially surfactant dysfunction disorders, pulmonary infections, primary ciliary dyskinesia, and cystic fibrosis. If a lung biopsy is performed, the tissue is typically characterized by (a) neuroendocrine cells (NEC) found in at least 75% of total airway profiles, (b) NEC representing at least 10% of epithelial airway profiles, and (c) large and/or numerous neuroepithelial bodies.¹² Usually minimal to no other pathogenic alterations, inflammatory cells or signs for fibrosis are present.^{8,10} If a lung biopsy is performed and fulfils the above mentioned criteria PTI is usually labelled NEHI.

Rauch et al⁷ found, that chest high-resolution computed tomography (HR-CT) is highly sensitive for PTI showing mainly ground glass opacities and only minor other abnormalities making lung biopsies only necessary in patients with contradictory findings. Depending on the distribution of ground glass opacities in HR-CT, PTI can be labelled as "PTI typical" or, if ground glass opacities are present in somewhat different distribution or in the presence of subtle minor abnormalities "PTI aberrant."^{7,13,14}

The etiology of PTI is still unknown. As some familial cases are published, a genetic susceptibility is suspected, but no disease-causing variant has been found yet.¹⁵ Some authors suggest additional environmental or host factors as the symptoms usually develop during the

first weeks of life.¹⁶ Others postulate a developmental delay as increased NEC can be found in the airways of the developing lung.¹⁷ Only case reports and small case series describing the clinical presentation and clinical course exist.^{7,16,18-20} To our knowledge, no death or lung transplantation has been described up to date. Treatment is mostly supportive, including supplemental oxygen and nutritional support (Table S1), but no standard therapies or guidelines are established.

In this study, we prospectively observed the clinical course of children older than 5 years that were diagnosed with PTI as infants.

2 | METHODS

2.1 | Patient selection

The Kids Lung Register is a web-based management platform that prospectively collects data of rare pediatric lung disorders with a focus on children's interstitial lung diseases (www.childeu.net).²¹ All patients included into the platform, presented with chILD defined by (a) typical symptoms or signs such as tachypnea and/or dyspnea, crackles, retractions, digital clubbing, failure to thrive, or respiratory failure (b) hypoxemia, and (c) diffuse radiological abnormalities present at diagnosis with a minimum duration of 4 weeks. The diagnosis of chILD is made in accordance with the clinical guidelines of the American Thoracic Society¹ and European management platform for interstitial lung diseases in children⁶ by a multidisciplinary team review board consisting of radiologists, pathologists, and clinicians with expertise in chILD.²¹ Included children with sufficient data set are diagnosed and categorized into the distinct categories and subcategories.⁶ Children reported to the Kids Lung Register, diagnosed with PTI and now older than 5 years were identified and included in the analysis. The clinical course of a relevant proportion of the patients during infancy was described before.⁷ Demographic data, information on the clinical presentation, severity of illness, radiological findings, treatment and outcome were prospectively collected. Recurrent aspirations and gastroesophageal reflux disease were evaluated in a step-wise approach. If patients had chronic wet cough or signs for a swallowing disorder, endoscopy, or barium swallow test was performed. During the observational period, the severity of illness was analyzed using adapted disease severity Fan score and categorized as (a) asymptomatic, (b) symptomatic, normal room air

oxygen saturation under all conditions, (c) symptomatic, normal resting room air saturation, but abnormal saturation (<90%) with sleep or exercise, (d) symptomatic, abnormal resting room air saturation (<90%), or (e) symptomatic with pulmonary hypertension.^{22,23} Age- and sex-specific z scores of spirometry data were calculated using the Global Lung Function Initiative reference values.²⁴ Normal values for respiratory rates derived by Fleming et al²⁵ were used.

2.2 | Radiology

HR-CT scans were systematically evaluated during the peer review process by radiologists with expertise in chest imaging specialized in interstitial lung diseases in children. To allow comparison with other studies a scoring system based on previous HR-CT studies was used.²⁶ Ground glass opacities located in the middle lobe, lingula, and the parahilar and paramediastinal distribution defined "PTI usual."²⁶ Ground glass opacities in other distributions or the presence of minor additional findings like small linear opacities or small consolidations (excluding dependent atelectasis) were considered "PTI aberrant" as published before.⁷ Due to lack of sufficient data on expiratory scans only inspiratory scans were analyzed.

2.3 | Histopathology and immunohistochemistry

Lung tissue was systematically evaluated during the peer review process of the Kids Lung Register by a pathologist specialized in interstitial lung diseases in children. The presence of NEC was determined by immunohistochemistry for bombesin in consecutive formalin-fixed sections. The number of immunopositive NECs, and bronchial epithelial cells were counted manually. NEHI was defined as mentioned above characterized by (a) NECs found in at least 75% of total airway profiles, (b) NEC representing at least 10% of epithelial airway profiles, and (c) large and/or numerous neuroepithelial bodies described in absence of other significant airway or interstitial lung disease.¹²

2.4 | Subgroups

The cohort was divided into three subgroups: (a) "PTI usual" and "PTI aberrant" defined as mentioned above, (b) "asymptomatic patients" (Fan score = 1) and "symptomatic patients" (Fan score ≥ 2), and (c) children with and without increased NECs in lung tissue defining NEHI.

2.5 | Ethics statement

All caregivers of the patients provided written informed consent and the participants' verbal assent to participate in the Kids Lung Register. The study was approved by the Ethics Commission at the Ludwig Maximilians University of Munich, Pettenkoferstr. 8, 80336 München (EK 026-06, 257-10, 111-13, 20-329).

2.6 | Statistical analysis

Data are presented as mean, standard deviation, and ranges. The statistical analysis was made using Graph Pad Prism (Version 8.0) and SPSS (Version 25). Means and their 95% confidence intervals were calculated. Frequency differences between groups were assessed using χ^2 test for categorical variable. A $P \leq .05$ level was considered statistically significant. Means of our sample z scores were considered significant different from the population, when their 95% confidence interval was outside the ± 1.96 range of the population's z score.

3 | RESULTS

3.1 | Study population

During the following observational period of mean of 3.94 years (range, 0.28-6.32) 35 patients older than 5 years of age, diagnosed with PTI as infants were included in the study (Figure 1). A total of 74% (26/35) were male. For all patients, pulmonary symptoms started within the first year of life (median age, 3.25 months; range, 0-12 months). Tachypnea was reported in all children, 74% (26/35) needed additional supplemental oxygen and 3% (1/35) invasive ventilation. A total of 26% (9/35) were diagnosed with additional abnormalities, like congenital heart defects (2/35), or muscular hypotonia (2/35). Further details of the study cohort are listed in Tables 1 and S2. A HR-CT scan of the lung was performed in every patient, whereas lung biopsy was performed in 46% (16/35; Table S3). No patient included in this study was rebiopsied.

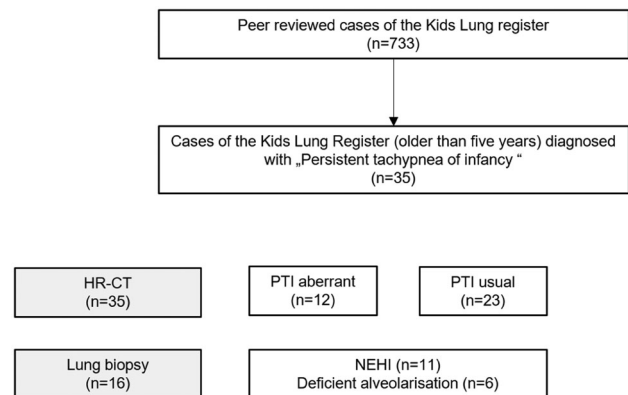


FIGURE 1 Subject allocation flow. Children with suspected interstitial lung diseases can be included in the Kids Lung Register. The cases are evaluated during a peer review by specialized physicians and allocated to a distinct category. Lung tissue with increased neuroendocrine cells is defining "NEHI." The subgroups "PTI usual" or "PTI aberrant" are defined by HR-CT scan of the lung showing GGO confined to middle lobe, lingula parahilar, and paramediastinal areas without additional abnormalities. HR-CT, high resolution computed tomography; NEHI, neuroendocrine cell hyperplasia of infancy; PTI, persistent tachypnea of infancy

TABLE 1 Medical history, vital signs, pulmonary function test, and treatment of cohort

Age of patients	5.0-5.9 y	6.0-6.9 y	7.0-7.9 y	8.0-8.9 y	9.0-9.9 y
Number of patients at follow up	31	17	12	9	5
Clinical presentation					
Chronic cough	2/31 (7)	1/17 (6)	2/12 (17)	-/9 (0)	1/5 (20)
Dyspnea	1/31 (3)	-/17 (0)	1/12 (8)	-/9 (0)	-/5 (0)
Tachypnea	3/31 (10)	1/17 (6)	2/12 (17)	1/9 (11)	-/5 (0)
Fine crackles (crepitations)	3/31 (10)	2/17 (12)	2/12 (17)	-/9 (0)	-/5 (0)
Gastroesophageal reflux	1/31 (3)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Recurrent aspirations	1/31 (3)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Pulmonary hypertension	1/31 (3)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Failure to thrive	4/31 (13)	-/17 (0)	-/12 (0)	1/9 (11)	-/5 (0)
Fan score^a					
1	23/31 (74)	13/17 (77)	10/12 (83)	7/9 (78)	4/5 (80)
2	4/31 (13)	2/17 (12)	1/12 (8)	1/9 (11)	1/5 (20)
3	3/31 (10)	2/17 (12)	1/12 (8)	1/9 (11)	-/5 (0)
4	-/31 (0)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
5	1/31 (3)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Pulmonary function test					
z score FEV1 (CI)	-0.92 (-1.47, -0.37)	-1.65 (-2.13, -1.17)	-1.21 (-2.00, -0.43)	-0.72 (-2.04, 0.06)	-1.22 (2.13, -0.31)
z score FVC (CI)	-1.10 (-1.56, -0.63)	-1.60 (-2.23, -0.97)	-0.98 (-1.96, -0.01)	-0.38 (-1.78, 1.02)	-1.00 (-2.84, 0.84)
z score MEF 25/75 (CI)	-0.69 (-1.23, -0.159)	-1.33 (-1.93, -0.72)	-1.00 (-2.03, 0.03)	-0.79 (-1.86, 0.29)	-1.56 (-4.83, 1.70)
z score FEV1/FVC (CI)	0.00 (-0.44, 0.45)	-0.04 (-0.81, 0.73)	-0.48 (-1.25, 0.29)	-0.53 (-1.53, 0.47)	-0.29 (-2.84, 2.27)
Treatment					
Glucocorticosteroids (inhaled)	6/31 (19)	2/17 (12)	3/12 (25)	3/9 (33)	1/5 (20)
Hydroxychloroquine	2/31 (7)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Macrolides (long term)	4/31 (13)	2/17 (12)	1/12 (8)	-/9 (0)	-/5 (0)
Others	2/31 ^b (7)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Nondrug treatment					
Oxygen supplementation	1/31 (3)	-/17 (0)	1/12 (8)	-/9 (0)	-/5 (0)
Noninvasive ventilation	-/31 (0)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Invasive ventilation	-/31 (0)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)
Surgery of intestine (PEG or PEJ)	-/31 (0)	-/17 (0)	-/12 (0)	-/9 (0)	-/5 (0)

Note: z scores are given in mean (95% confidence interval). All other data are shown as numbers of subjects and their percentage (n (%))

Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MEF, mean expiratory flow; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.

^aFan score: (1) asymptomatic, (2) symptomatic, normal room air oxygen saturation under all conditions, (3) symptomatic, normal resting room air saturation, but abnormal saturation (<90%) with sleep or exercise, (4) symptomatic, abnormal resting room air saturation (<90%), (5) symptomatic with pulmonary hypertension.

^bSalmeterol/fluticasone and NaCl 3% by inhalation.

3.2 | Clinical characteristics, lung function, and treatment during follow-up

At 5 years of age, the data of 31 patients were available and four children missed the clinical follow up at that age (Table 1). At this age, Fan score of 1 indicated that 74% (23/31) were asymptomatic. A total of 13% (4/31) had a Fan score of 2, 10% (3/31) a Fan score of 3 and 3% (1/31) a Fan score of 5. The clinical course improved. At the age of 9 years only one patient was reported symptomatic, but with normal oxygen saturation (Table 1).

In symptomatic patients, the most common symptoms and conditions reported were tachypnea, fine crackles, and chronic cough. If, at the start of the observational period tachypnea and fine crackles were found, it was reported consistently until improvement. Whereas, if chronic cough was reported, it presented intermittent (max. 1 year). In none of the patients that were asymptomatic at 5 years the clinical course deteriorated (Table 1 and Figure 2A). No additional, other complications occurred. During the observational period, no patients had wheezing, hemoptysis, or recurrent lower airway infections.

At the age of 5 years, a relevant proportion of the patients received different treatment: 19% (6/31) were treated with inhaled glucocorticosteroids, 13% (4/31) with long-term macrolides, and 7% (2/31) with hydroxychloroquine. Except for inhaled glucocorticosteroids, all other drugs were discontinued during the observation period. Based in the data available, no drug had a clear effect on the clinical course.

During the observational period, analyses of lung function data and respiratory rate were within normal values (Table 1 and Figure 2B-E). There was no correlation between clinical course, pulmonary function tests and treatment of the patients. No infant pulmonary functions tests were performed.

3.3 | Comparison between subgroups

Explorative analysis of the clinical courses, pulmonary function tests, and treatment showed no differences between the subgroups "PTI usual" and "PTI aberrant." Symptomatic and asymptomatic patients were equally distributed between both groups (Tables S2, S3, and S4a/b). "PTI aberrant" had more congenital heart defects than patients with "PTI usual" ($P = .044$). At the age of 5 years, additional muscular hypotonia was more often diagnosed with symptomatic patients ($P < .001$). No differences regarding the clinical course, pulmonary function tests and treatment were found between children with or without histologic proven NEHI (Tables S2, S3, and S4a/b). Sex had no influence on the presentation or clinical course.

4 | DISCUSSION

This study analyzed a cohort of children diagnosed with PTI from school-age. At the age of 5 years, the majority of children were asymptomatic. During the observational period, in most of the symptomatic patients the clinical course improved and at the age of 9 years, no patients had abnormal oxygen saturation in sleep or during exercise anymore. In no patients the clinical course deteriorated.

Lung function tests and breathing frequency were within normal values throughout the complete observational period. This is in line with previously reported normal spirometry results in children at school age.¹⁰ With infant pulmonary function tests and body plethysmography, however, airway obstruction and hyperinflation has been reported before.^{16,27,28} The exact mechanism of the impaired lung function is not known yet. Some authors suggested an increased level of bioactive peptides produced by the NECs as origin.^{16,29} Still, in urine we could not find any differences of bombesin excretion between controls or infants diagnosed with PTI.⁷ Consistently, no differences were found between the subgroups "PTI usual" and "PTI aberrant" or the presence of increased NECs in lung tissue defining NEHI. Caution is necessary, as the number of children allocated to one of the subgroups was low.

Clinicians had treated about almost 20% of the children with various treatments (Table S1). In particular, younger patients were

treated mostly with inhaled glucocorticosteroids, few with macrolides or hydroxychloroquine for extended periods. However the role of this treatment on the clinical course was difficult to analyze. The impact of such treatments should be evaluated to establish guidelines.

Major strength of this study is the systematic and prospective observation of relatively large cohort of patients with a single, rare chILD entity only known for the last 20 years. There are some limitations of the current study to consider. As this is not a population-based study, mild clinical courses may not be reported to the Kids Lung Register and thus completely excluded from this analysis. More elaborated techniques such as body plethysmography for assessment of total lung volume and

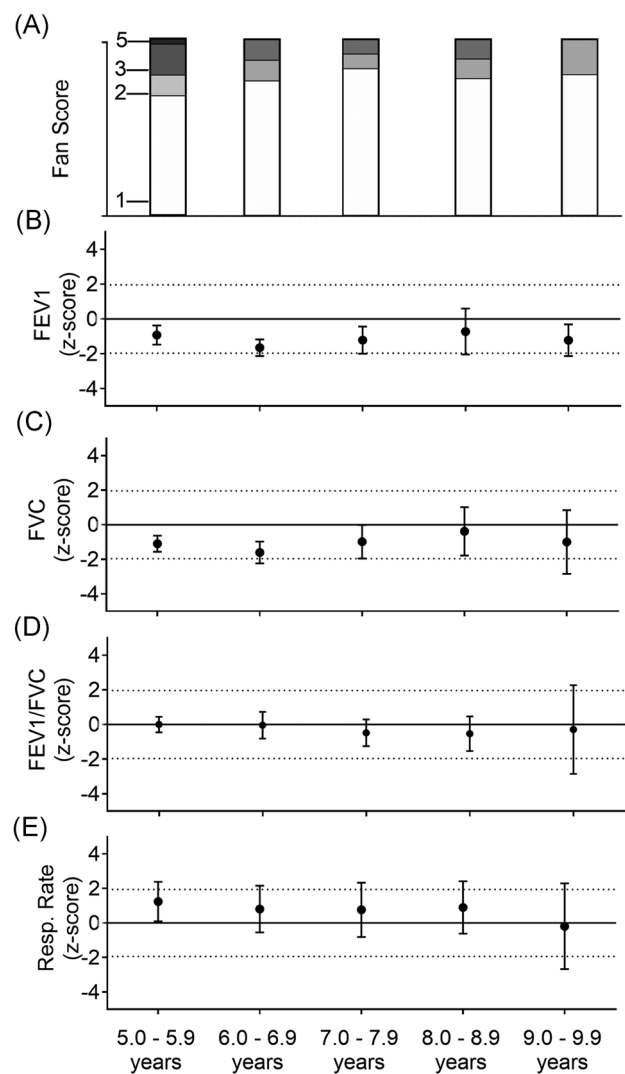


FIGURE 2 A, Fan scores and z scores of lung function values for (B) FEV 1, (C) FVC, (D) mean expiratory flow 25% to 75% (MEF 25/75), (E) FEV1/FVC ratio and (F) respiratory rate during observation period. Solid lines represent the mean 95% confidence interval. The dotted line at 1.96 and -1.96 represent the limit of statistical significance ($P < .05$). FEV 1, forced expiratory volume in 1 second; FVC, forced vital capacity

hyperinflation, or the use of multiple breath washout to detect mild ventilation heterogeneity, might demonstrate pulmonary function abnormalities, we missed by routine spirometry.

Fortunately, our study demonstrates that, at school age most of the children previously chronically affected infants became asymptomatic and pulmonary function tests as well as measurements of the breathing frequency were within normal values. Only a small proportion of the children were reported as symptomatic. The knowledge of having a chronic pulmonary disease might have an impact on the reporting of symptoms and common population symptoms such as cough could be attributed to PTI. We conclude that at school age the overall clinical course of PTI is favorable.

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REFERENCES

- Kurland G, Deterding RR, Hagood JS, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med*. 2013;188:376-394. <https://doi.org/10.1164/rccm.201305-0923ST>
- Deutsch GH, Young LR, Deterding RR, et al. Diffuse lung disease in young children: application of a novel classification scheme. *Am J Respir Crit Care Med*. 2007;176:1120-1128. <https://doi.org/10.1164/rccm.200703-393OC>
- Das S, Langston C, Fan LL. Interstitial lung disease in children. *Curr Opin Pediatr*. 2011;23:325-331. <https://doi.org/10.1097/MOP.0b013e3283464a37>
- Griese M, Haug M, Brasch F, et al. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. *Orphanet J Rare Dis*. 2009;4:26. <https://doi.org/10.1186/1750-1172-4-26>
- Kornum JB, Christensen S, Grijota M, et al. The incidence of interstitial lung disease 1995-2005: a Danish nationwide population-based study. *BMC Pulm Med*. 2008;8:24. <https://doi.org/10.1186/1471-2466-8-24>
- Griese M, Irnstetter A, Hengst M, et al. Categorizing diffuse parenchymal lung disease in children. *Orphanet J Rare Dis*. 2015;10:122. <https://doi.org/10.1186/s13023-015-0339-1>
- Rauch D, Wetzke M, Reu S, et al. Persistent tachypnea of infancy. Usual and aberrant. *Am J Respir Crit Care Med*. 2016;193:438-447. <https://doi.org/10.1164/rccm.201508-1655OC>
- Deterding RR, Fan LL, Morton R, Hay TC, Langston C. Persistent tachypnea of infancy (PTI)—a new entity. *Pediatr Pulmonol Suppl*. 2001; 23:72-73.
- Hull J, Chow CW, Robertson CF. Chronic idiopathic bronchiolitis of infancy. *Arch Dis Child*. 1997;77:512-515. <https://doi.org/10.1136/adc.77.6.512>
- Deterding RR, Pye C, Fan LL, Langston C. Persistent tachypnea of infancy is associated with neuroendocrine cell hyperplasia. *Pediatr Pulmonol*. 2005;40:157-165. <https://doi.org/10.1002/ppul.20243>
- Nevel RJ, Garnett ET, Schaudies DA, Young LR. Growth trajectories and oxygen use in neuroendocrine cell hyperplasia of infancy. *Pediatr Pulmonol*. 2018;53:656-663. <https://doi.org/10.1002/ppul.23958>
- Dishop MK. Paediatric interstitial lung disease: classification and definitions. *Paediatr Respir Rev*. 2011;12:230-237. <https://doi.org/10.1016/j.prrv.2011.01.002>
- Brody AS, Crotty EJ. Neuroendocrine cell hyperplasia of infancy (NEHI). *Pediatr Radiol*. 2006;36:1328. <https://doi.org/10.1007/s00247-006-0302-3>
- Spielberg DR, Brody AS, Baker ML, Woods JC, Towe CT. Ground-glass burden as a biomarker in neuroendocrine cell hyperplasia of infancy. *Pediatr Pulmonol*. 2019;54:822-827. <https://doi.org/10.1002/ppul.24301>
- Popler J, Gower WA, Mogayzel PJ Jr, et al. Familial neuroendocrine cell hyperplasia of infancy. *Pediatr Pulmonol*. 2010;45:749-755. <https://doi.org/10.1002/ppul.21219>
- Lukkarinen H, Pelkonen A, Lohi J, et al. Neuroendocrine cell hyperplasia of infancy: a prospective follow-up of nine children. *Arch Dis Child*. 2013;98:141-144. <https://doi.org/10.1136/archdischild-2012-302115>
- Bush A, Griese M, Seidl E, Kerem E, Reu S, Nicholson AG. Early onset children's interstitial lung diseases: discrete entities or manifestations of pulmonary dysmaturity? *Paediatr Respir Rev*. 2019;30:65-71. <https://doi.org/10.1016/j.prrv.2018.09.004>
- Gomes VC, Silva MC, Maia Filho JH, et al. Diagnostic criteria and follow-up in neuroendocrine cell hyperplasia of infancy: a case series. *J Bras Pneumol*. 2013;39:569-578. <https://doi.org/10.1590/S1806-37132013000500007>
- Nevel RJ, Garnett ET, Worrell JA, et al. Persistent lung disease in adults with NKX2.1 mutation and familial neuroendocrine cell hyperplasia of infancy. *Ann Am Thorac Soc*. 2016;13:1299-1304. <https://doi.org/10.1513/AnnalsATS.201603-155BC>
- O'Connor MG, Wurth M, Young LR. Rare becomes more common: recognizing neuroendocrine cell hyperplasia of infancy in everyday pulmonary consultations. *Ann Am Thorac Soc*. 2015;12:1730-1732. <https://doi.org/10.1513/AnnalsATS.201507-422LE>
- Griese M, Seidl E, Hengst M, et al. International management platform for children's interstitial lung disease (chILD-EU). *Thorax*. 2018;73: 231-239. <https://doi.org/10.1136/thoraxjnl-2017-210519>
- Fan LL, Kozinetz CA. Factors influencing survival in children with chronic interstitial lung disease. *Am J Respir Crit Care Med*. 1997;156: 939-942. <https://doi.org/10.1164/ajrccm.156.3.9703051>
- Fan LL, Langston C. Chronic interstitial lung disease in children. *Pediatr Pulmonol*. 1993;16:184-196. <https://doi.org/10.1002/ppul.1950160309>
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324-1343. <https://doi.org/10.1183/09031936.00080312>
- Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 2011;377: 1011-1018. [https://doi.org/10.1016/S0140-6736\(10\)62226-X](https://doi.org/10.1016/S0140-6736(10)62226-X)
- Brody AS, Guillerman RP, Hay TC, et al. Neuroendocrine cell hyperplasia of infancy: diagnosis with high-resolution CT. *AJR Am J Roentgenol*. 2010;194:238-244. <https://doi.org/10.2214/AJR.09.2743>
- Kerby GS, Wagner BD, Popler J, et al. Abnormal infant pulmonary function in young children with neuroendocrine cell hyperplasia of infancy. *Pediatr Pulmonol*. 2013;48:1008-1015. <https://doi.org/10.1002/ppul.22718>
- Young LR, Brody AS, Inge TH, et al. Neuroendocrine cell distribution and frequency distinguish neuroendocrine cell hyperplasia of infancy

from other pulmonary disorders. *Chest*. 2011;139:1060-1071. <https://doi.org/10.1378/chest.10-1304>

29. Cutz E, Yeger H, Pan J. Pulmonary neuroendocrine cell system in pediatric lung disease-recent advances. *Pediatr Dev Pathol*. 2007;10:419-435. <https://doi.org/10.2350/07-04-0267.1>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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