Diagnostic Evaluation and Clinical Findings in Children With Persistent Tachypnea of Infancy/Neuroendocrine Cell Hyperplasia of Infancy

A European Multicenter Retrospective Study

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BACKGROUND: Persistent tachypnea of infancy (PTI) or neuroendocrine cell hyperplasia of infancy (NEHI) is a form of childhood interstitial lung disease (chILD) that predominantly affects young children. Although it is one of the most common chILDs, no unified diagnostic approach specific to this condition exists.

RESEARCH QUESTION: Are the clinical presentation and the diagnostic approach different in patients with PTI/NEHI among European countries?

STUDY DESIGN AND METHODS: This was a European multicenter, retrospective, observational study. Data on clinical characteristics and diagnostic strategies in patients with PTI/NEHI were analyzed and compared across participating countries.

RESULTS: The study included 378 children with PTI/NEHI from 17 countries (63.5% male, 97.4% White) who received a diagnosis at a median age of 9 months (interquartile range, 6-13 months). The most common baseline symptoms were tachypnea, chest retractions, crackles on auscultation, hypoxemia, and failure to thrive. High-resolution CT (HRCT) imaging was performed in all patients, with most undergoing chest radiography, echocardiography, and immunology tests. Lung biopsy was carried out in 23.5% of patients, with a decreasing trend over time and variation by country; its use was associated with longer diagnostic delay. Histopathologic examination showed a hyperplasia of pulmonary neuroendocrine cells in 52.8% of patients. Genetic testing was rare, and its application varied significantly among countries. Additional investigations that do not have an established role, such as assessment for gastroesophageal reflux disease and OSA, infant pulmonary function tests, and lung ultrasound, were limited to single countries.

INTERPRETATION: Diagnosis of PTI/NEHI relies on clinical symptoms and HRCT imaging results, with lung biopsies less commonly performed. Differences exist among countries regarding the number and type of investigations. A need exists for guidelines that will standardize the diagnostic approach. CHEST 2025; ■(■):■-■

KEY WORDS: childhood interstitial lung disease; chILD; NEHI; neuroendocrine cell hyperplasia of infancy; persistent tachypnea of infancy; PTI

ABBREVIATIONS: chILD = childhood interstitial lung disease; GERD = gastroesophageal reflux disease; GGO = ground glass opacity; HRCT = high-resolution CT; IQR = interquartile range; LUS = lung ultrasound; NEHI = neuroendocrine cell hyperplasia of infancy; PFT = pulmonary function test; PNEC = pulmonary neuroendocrine cell; PTI = persistent tachypnea of infancy

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DOI: https://doi.org/10.1016/j.chest.2025.02.023

Take-Home Points

Study Question: Do differences exist in the clinical presentation and the diagnostic approach in patients with persistent tachypnea of infancy (PTI) or neuroendocrine cell hyperplasia of infancy (NEHI) among European countries?

Results: Across all participating countries, PTI/NEHI diagnosis primarily relies on characteristic clinical symptoms and chest high-resolution CT imaging findings, with a declining reliance on lung biopsy. However, significant variations exist in the number and type of additional tests performed.

Interpretation: A need exists to establish uniform recommendations for PTI/NEHI that outline the basic minimum diagnostic requirements to avoid the use of tests with limited diagnostic value.

Persistent tachypnea of infancy (PTI) or neuroendocrine cell hyperplasia of infancy (NEHI) is a rare disease classified in the broad spectrum of childhood interstitial lung diseases (chILDs). Its clinical features were described first in 1997.[1] In 2001, Deterding et al[2] provided a more detailed description and introduced the term *PTI*. The condition was defined further as NEHI after the identification of a high number of pulmonary neuroendocrine cells (PNECs) in the distal bronchioles of affected patients.[3] Given the rare use of lung biopsies to demonstrate PNECs in current practice and the fact that not all biopsies reveal a high number of PNECs, *PTI* is a more accurate term.[4] Because the term *NEHI* is used commonly by some authors regardless of lung biopsy confirmation, we use the collective term *PTI/NEHI* in this article.[5-7] The exact prevalence of PTI/NEHI is unknown. Studies conducted to date indicate that it accounts for 12% to 23% of all chILDs.[5,8-11] Clinical symptoms principally include tachypnea, chest retractions, crackles on auscultation, hypoxemia, and failure to thrive, which typically begin in early infancy.[3,12] The prognosis for PTI/NEHI generally is favorable compared with that of other chILDs, with most children experiencing gradual improvement over time. Notably, no cases of mortality or pulmonary hypertension have been reported.[4] However, the condition can have a significant impact on daily life in the early years, primarily because of the need for prolonged oxygen therapy during sleep and, in severe cases, continuously.[12] In addition, some children may experience persistent respiratory symptoms and impaired lung function in the long term.[13]

Despite expanding knowledge about this disease, diagnostic practices are still not uniform. Management strategies are based on retrospective analyses of case series, with the largest cohort consisting of 199 children from the United States.[2,3,6,14-18] A diagnostic approach typically involves a comprehensive clinical evaluation followed by high-resolution CT (HRCT) imaging of the chest. Originally, a lung biopsy was performed to establish a diagnosis.[1,3] In 2010, Brody et al[19] demonstrated that chest HRCT imaging showing ground-glass opacities (GGOs) in the middle lobe, lingula, and paramediastinal regions associated with areas of air trapping were highly indicative of NEHI. Therefore, it was suggested that lung biopsy should be reserved for patients with unusual clinical or radiologic features. Additionally, genetic testing, particularly to exclude pathogenic variants in the *NKX2.1* or *FOXP1* genes, is suggested.[4,20] Also some evidence supports the importance of testing for comorbidities such as OSA, gastroesophageal reflux disease (GERD), and immunodeficiency.[6,21,22] Additionally, single studies have demonstrated the application of infant pulmonary function tests and lung ultrasound (LUS) in the diagnostic approach.[7,23,24]

Given the results of these studies, we sought to determine if a difference exists in the clinical presentation of and the diagnostic approach toward patients with PTI/NEHI among European countries. We hypothesized that such differences are present.

Study Design and Methods

Study Design and Data Collection

This was a multicenter, retrospective, observational study of patients with PTI/NEHI. Members of the European Respiratory Society Clinical Research Collaboration chILD-EU, who manage patients with chILD, were invited to enroll eligible individuals. Data were obtained from 2 sources: retrieved from the prospectively collected data in the web-based chILD-EU Registry (www.childeu.net) and from datasheets completed by centers not using the registry.[10] The datasheet included information on birth and family history, symptoms, and diagnostic approach. Data were collected from January through December 2023. All data were collected

anonymously. The bioethics committee of the Medical University of Warsaw, Poland, approved the study (Identifier: AKBE/91/2021). All participants included in the study via the chILD-EU Registry consented therein, and the data merge was approved by the central ethics committee in Munich, Germany (Identifier: EK23-0962).

Study Population

Patients with PTI/NEHI were included. The diagnosis was established by a participating center according to American Thoracic Society clinical practice guidelines and was based on clinical characteristics (persistent tachypnea, retractions, hypoxemia, crackles, or a combination thereof) combined with typical chest HRCT imaging findings, which include the presence of GGOs in at least the middle lobe and lingula (less extensive changes) or in the middle lobe, lingula, and paramediastinal regions (more extensive changes).[2,3,25] Exclusion criteria included incomplete data collection (< 80% of required information) and the presence of a genetic variant associated with a different disease.

Variables

The age at diagnosis, symptoms, and diagnostic procedures were compared among countries that contributed at least 10 patients. Diagnostic delay also was compared between children who underwent lung biopsy and those who did not. Additionally, the number of lung biopsies was analyzed for patients who received a diagnosis before and after 2010. That year, Brody et al[19] demonstrated the high sensitivity and specificity of HRCT imaging in diagnosing NEHI.

Based on the collected data, the NEHI Clinical Score proposed by Liptzin et al[6] was evaluated. This tool comprises 10 criteria, each worth 1 point: symptom onset before 12 months, failure to thrive, no clubbing, no cough, no wheezing, chest wall abnormalities, crackles, hypoxemia, tachypnea, and retractions. A score of ≥ 7 of 10 was considered positive for the condition.

Statistical Analysis

Comparisons between continuous variables were made using the nonparametric Mann-Whitney *U* test, whereas comparisons between multiple quantitative variables were made using the nonparametric Kruskal-Wallis test. Post hoc analysis (the Dunn test) was performed to assess differences among countries. Logistic regression was used to evaluate which symptoms increase the odds of more extensive GGOs on HRCT imaging. Statistical analysis was performed using GraphPad Prism version 10.2.2 software (GraphPad Software).

Results

Of the 397 patients initially included in the study, data from 378 patients with PTI/NEHI were analyzed, with the number per country ranging from 1 to 137 (17 countries, 73 centers) (Fig 1). Table 1 summarizes the characteristics of the study group. Most patients were male (63.5%) and White (97.4%), born at term (90.3%), and in good condition. The median age at diagnosis was 9 months (interquartile range [IQR], 6-13 months), and the median diagnostic delay was 4 months (IQR, 2-8 months). Diagnostic delay was significantly longer in children who received a diagnosis before 2010 compared with those who received a diagnosis after 2010 (median, 8 months vs 4 months; $P = .0003$). Tachypnea, chest retractions, crackles, hypoxemia, and failure to thrive were the most frequent baseline symptoms. Chest deformities were reported in 101 patients, with barrel chest being the most common (Table 2).

Table 3 summarizes the investigations performed in the study group.[25,26] All children underwent chest HRCT scans at a median age of 8 months (IQR, 5-12 months). In 30.4% of patients, chest radiographs showed normal results. Patients with less extensive GGOs on HRCT imaging were significantly more likely to show normal chest radiograph results (OR, 1.8; 95% CI, 1.11-3.17). However, normal chest radiograph findings did not exclude the presence of more extensive abnormalities. Among 102 patients with normal chest radiograph results, 66 patients (64.7%) showed extensive changes on HRCT imaging. Lung biopsy was performed in 89 patients at a median age of 10 months (IQR, 7-20 months). The procedure was significantly less common in patients who received a diagnosis after 2010 compared with those who received a diagnosis before 2010 (18.0% vs 71.8%; $P < .00001$). No significant differences were found in the extent of GGOs on HRCT imaging ($P = .782$) or the presence of additional changes ($P = .252$) between children with NEHI features on lung biopsy and those without. The median diagnostic delay was longer in children who underwent lung biopsy compared with those who did not (6 months vs 4 months; $P < .00001$). Asymptomatic minor echocardiographic abnormalities were observed in 23.1% of patients, and no cases of pulmonary

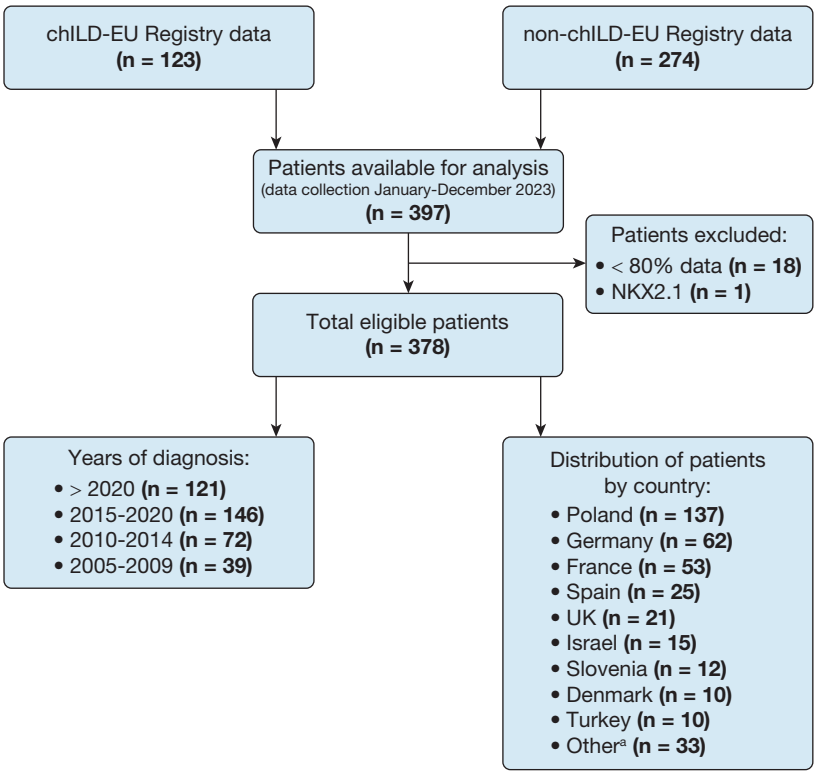

Figure 1 – *Study flowchart showing distribution of enrolled patients by country.* [a]*Patients from countries who contributed fewer than 10 patients (Switzerland, Greece, Austria, Italy, Belgium, Hungary, Czech Republic, and The Netherlands). chILD = childhood interstitial lung disease.*

hypertension were diagnosed. All patients who underwent genetic analysis showed negative results or had benign variants identified.

Of the patients for whom the NEHI Clinical Score could be calculated (available data for all 10 components), most patients (86.5%) scored ≥ 7 points. Children with more extensive GGOs more often had a NEHI Clinical Score of ≥ 7 ($P = .00012$), and an NEHI Clinical Score of ≥ 7 increases the odds of having more extensive GGOs on HRCT imaging (OR, 4.85; 95% CI, 2.16-10.88) (Table 4).

Comparisons Among Countries

Significant differences in the frequency of symptoms were observed among countries, except for tachypnea. Also considerable variation was found in the use of diagnostic tests (Fig 2), the time of diagnosis, and diagnostic delay among countries (Table 5).

Discussion

This European study provided data on clinical findings and diagnostic evaluation of, to our knowledge, the largest cohort of children with PTI/NEHI described to date. Currently, diagnosis of PTI/NEHI relies on clinical symptoms and chest HRCT imaging, with lung biopsy less commonly performed. Significant differences in diagnostic approach exist among countries, particularly in the number and types of tests performed.

The clinical characteristics observed in this cohort of patients with PTI/NEHI are consistent with those reported in previous studies.[3,6,12,16,27] Tachypnea, chest retractions, crackles, hypoxemia, and failure to thrive were the most common symptoms reported in all countries. Additionally, cough and wheezing at baseline were observed quite frequently in some countries. Because approximately 40% of cases of PTI/NEHI were diagnosed in the peri-infectious period, it may be assumed that this influenced the frequency of these symptoms. In this cohort, the most common chest abnormality was barrel chest, which may be attributed to hyperinflation and air trapping.[28] The presence of such abnormalities in PTI/NEHI has been demonstrated through pulmonary function tests and radiologic findings.[7,13,24,29,30] Similarly to the findings by Liptzin et al,[6] in our study, a high prevalence of pectus excavatum and pectus carinatum was reported. These deformities may result from chest retractions that affect the weaker anterior cartilaginous regions of the chest and alter the structure of the chest wall in infants. Younger age at symptom onset has been associated with a higher prevalence of chest wall deformities.[31]

TABLE 1] Characteristics of Included Patients

Variable	Data
Sex (n = 378)	
Male	240 (63.5)
Female	138 (36.5)
Race (n = 352)	
White	343 (97.4)
Black	9 (2.6)
Birth history	
Gestational age at birth, wk (n = 371)	39 (38-40)
Route of delivery (n = 275)	
Vaginal birth	182 (66.2)
Cesarean section	93 (33.8)
Apgar score (n = 186)	10 (9-10)
Birth weight, g (n = 331)	3,356 (3,000-3,655)
Neonatal respiratory distress (n=373)[a]	51 (13.7)
Family history	
Consanguinity (n = 374)	12 (3.2)
Parental ILD (n = 367)	10 (2.7)
PTI/NEHI	1 (0.3)
Other[b]	9 (2.5)
Sibling ILD (n = 201)	19 (9.5)
PTI/NEHI	17 (8.5)
Other[b]	2 (1.0)
Diagnosis	
Age at onset of symptoms, mo (n = 378)	4 (2-6)
Onset of the disease (n = 324)	
Peri-infectious	126 (38.9)
Insidious	197 (61.1)
Age at diagnosis, mo (n = 378)	9 (6-13)
Diagnostic delay, mo (n = 378)	4 (2-8)

Data are presented as No. (%) of patients with available data or median (interquartile range). ILD = interstitial lung disease; NEHI = neuroendocrine cell hyperplasia of infancy; PTI = persistent tachypnea of infancy.
[a]Transient respiratory insufficiency, inborn pneumonia, apnea associated with prematurity, and pneumothorax.
[b]Sarcoidosis, hypersensitivity pneumonitis, and unspecified ILD.

TABLE 2] Symptoms at the Onset of Disease

Symptoms	No. (%)
Tachypnea (n = 378)	367 (97.1)
Retractions (n = 370)	348 (94.1)
Crackles (n = 370)	291 (78.6)
Oxygen saturation (n = 378)	
Normal under all conditions	91 (24.1)
Abnormal (< 92%) with sleep or exercise	250 (66.1)
Abnormal at rest	23 (6.1)
Abnormal during infections	14 (3.7)
Failure to thrive (n = 370)[a]	170 (45.9)
Chest wall deformity (n = 247)[b]	101 (40.9)
Cough (n = 372)	73 (19.6)
Wheezing (n = 346)	66 (19.1)
Developmental delay (n = 370)[c]	35 (9.5)
Feeding difficulties (n = 370)[d]	16 (4.3)

Data are presented as No. (%) of patients with available data.
[a]BMI less than the 5th percentile on World Health Organization growth charts.
[b]Barrel chest (48.5%), pectus excavatum (18.8%), pectus carinatum (6.8%), and not specified (25.7%).
[c]Delayed milestones, poor coordination or hypotonia, and limited speech.
[d]Difficulty latching or sucking or repeated choking, coughing, or gagging during feeding.

Liptzin et al[6] proposed the NEHI Clinical Score as a sensitive tool to assist clinicians in identifying patients who may require further evaluation for NEHI, with a score of ≥ 7 achieving a sensitivity of 93%. In our study, 86.5% of patients had a score ≥ 7, and 13.5% of those with a PTI/NEHI diagnosis scored < 7. This highlights the potential for missed diagnoses when relying solely on the NEHI Clinical Score. We observed that 82.9% of patients with an NEHI Clinical Score of ≥ 7 showed more extensive GGO compared with only 50% of patients with a score of < 7. This is consistent with the findings of Spielberg et al,[32] who reported a correlation between the extent of GGO and symptom severity, reinforcing that less severe symptoms are associated with less intense GGO. Our results suggest that the NEHI Clinical Score should be interpreted with caution. A positive NEHI Clinical Score reinforces the diagnostic suspicion of PTI/NEHI, whereas a negative score does not exclude the disease, particularly in patients with fewer symptoms. Prospective studies are needed to evaluate the predictive accuracy of this clinical tool.

The chest radiograph is the most common initial radiologic investigation to evaluate persistent respiratory symptoms, but lacks sensitivity in detecting interstitial lung diseases.[20] Normal chest radiograph findings do not exclude the presence of interstitial lung disease. In the present cohort, 30.4% of patients showed no abnormalities, although some of them showed extensive GGOs on chest HRCT imaging. This discrepancy is likely because of the limited visibility of the paramediastinal regions on conventional radiography. HRCT imaging provides a higher degree of confidence when diagnosing interstitial lung disease.[20] In the

TABLE 3] Investigations Performed at the Time of Diagnosis

Investigation	No. of Performed Investigations (%)
Chest HRCT imaging (n = 378)	
GGOs in the middle lobe and lingula	378 (100)
GGOs in the middle lobe, lingula, and paramediastinal regions	292 (77.2)
Air trapping[a]	112 (29.6)
Additional findings[b]	130 (34.4)
Chest radiography (n = 335)	
Abnormal (parahilar markings, hyperinflation, or both[c])	233 (69.6)
Lung biopsy (n = 89)	
High PNECs number[25,26]	47 (52.8)
No abnormalities or mild inflammation	36 (40.4)
No PNECs staining	6 (6.7)
LUS (n = 74)	
Abnormal (B-line artefacts, pleural irregularities, or both)	61 (82.4)
Echocardiography (n = 334)	
Abnormal (minor defects)	77 (23.1)
Patent foramen ovale	46 (13.8)
Atrial septal defect II	11 (3.3)
Other[d]	20 (5.9)
Immunology tests (n = 319)	
Abnormal (minor defects)	61 (19.1)
Mild decrease in complement C3 or C4	26 (8.2)
Transient hypoglobulinemia	16 (5.0)
Neutropenia	11 (3.4)
IgA deficiency	8 (2.5)
Bronchoscopy (n = 193)	
Abnormalities (minor)	61 (31.6)
Elevated neutrophil or lymphocyte count on BAL	51 (26.4)
Mild tracheomalacia	7 (3.6)
Mild laryngeal abnormalities	3 (1.6)
Genetic analysis (n = 187)	
Sequencing[e]	32 (17.1)
Exclusive screening for the *NKX2.1*	155 (82.9)
pH monitoring (n = 133)	
GERD	56 (42.1)
IPFTs (n = 38)	
Abnormal (mixed airflow limitation, air trapping)	26 (68.4)
Polysomnography (n = 106)	
OSA	69 (65.1)

BAL = bronchoalveolar lavage; GERD = gastroesophageal reflux disease; GGO = ground glass opacity; HRCT = high-resolution CT; IPFT = infant pulmonary function test; LUS = lung ultrasound; PNEC = pulmonary neuroendocrine cell.

[a]Air trapping evaluated on expiratory images.

[b]Minor parenchymal infiltrations and bronchial thickening.

[c]Radiolucency, flattened hemidiaphragmatic contours, and horizontalization of ribs.

[d]Minor valve defects, small ventricular septal defect, anomalous right subclavian artery, and patent ductus arteriosus.

[e]The extent of genes tested via sequencing varied between countries, ranging from surfactant metabolism genes only to a wide range of genes associated with interstitial lung disease and whole genome sequencing.

TABLE 4] HRCT Imaging Findings in Patients Scoring ≥ 7 and < 7 Points in the NEHI Clinical Score

HRCT Imaging Findings	NEHI Clinical Score	
	≥ 7 (n = 193 [86.5%])	< 7 (n = 30 [13.5%])
GGOs limited to the middle lobe and lingula (n = 48 [21.5%])	33 (17.1)	15 (50.0)
GGOs in the middle lobe, lingula, and paramediastinal regions (n = 175 [78.5%])	160 (82.9)	15 (50.0)

Data are presented as No. (%) for patients with available data for all NEHI Clinical Score components (n = 223). GGO = ground glass opacity; HRCT = high-resolution CT; NEHI = neuroendocrine cell hyperplasia of infancy.

present study, all patients underwent a chest HRCT imaging, and all exhibited the presence of GGOs in at least the middle lobe and lingula. Notably, additional changes were reported in more than one-third of the patients. Abnormalities included parenchymal infiltrations and bronchial thickening, which may be associated with a concomitant infection. In addition, mild GGOs in locations atypical of PTI/NEHI were reported. Similarly, Rauch et al[15] reported additional HRCT imaging abnormalities that did not alter the clinical course of PTI/NEHI. LUS has emerged as a valuable tool for diagnosing and monitoring various pulmonary diseases. Urbankowska et al[23] demonstrated in children with PTI/NEHI that enhanced pleural thickness and increased number of B-lines correlated with HRCT imaging findings. Follow-up assessments at 6 and 12 months after inclusion showed no significant change in LUS findings. Despite its potential, LUS has not been adopted widely in clinical practice. Our data indicate that its use remains limited to a small number of patients in 3 countries. Although LUS has high sensitivity, it lacks specificity and cannot be used to establish a diagnosis. However, it may be a promising, radiation-free tool for disease follow-up. More studies are needed to evaluate its usefulness further.

Initially, the identification of a high number of PNECs in lung biopsy specimens—specifically, PNECs present in ≥ 70% of bronchioles and ≥ 10% in a single airway—was considered the most important criterion for diagnosis.[25,26] Since the high diagnostic value of HRCT imaging in PTI/NEHI was established, the number of lung biopsies has decreased substantially.[19] Our study demonstrated, that after 2010, only 18.0% of patients underwent this procedure. The usefulness of lung biopsy is questioned further by the fact that not all patients with typical symptoms and radiologic PTI/NEHI features fulfill the histopathologic criteria. Moreover, the number of PNECs may vary between biopsy sites in the same patient.[27] In our study, histopathologic criteria for PTI/NEHI were met in only 52.8% of children. These results are consistent with previous studies reporting that only 50% to 70% of patients with PTI/ NEHI who underwent biopsy had a high number of PNECs.[15,33,34] Furthermore, no correlation is observed between GGO density and the number of PNECs, further diminishing the relevance of lung biopsy in the diagnostic approach.[34] Importantly, our data indicate that performing a lung biopsy is associated with a longer diagnostic delay. These results collectively support the view that lung biopsy should not be a routine diagnostic test. It is suggested that it should be reserved for patients with atypical clinical presentations.[4,15]

A total of 18 confirmed cases of PTI/NEHI were identified among close relatives, which may suggest a possible genetic predisposition. However, no specific genetic variant causing PTI/NEHI has been identified to date. It is important to note the existence of diseases with known pathogenic variants, such as *NKX2.1* and *FOXP1*, whose clinical and radiologic presentations may resemble PTI/NEHI.[35,36] Although the clinical course of these diseases initially may seem similar to PTI/NEHI, they are distinct entities that require different diagnostic and therapeutic approaches. *NKX2.1* leads to brain-lung-thyroid syndrome, which manifests with choreoathetosis and congenital hypothyroidism and may present with pulmonary dysfunction. Intellectual disability with speech impairment without autistic features is associated with *FOXP1*. Therefore, testing for *NKX2.1* and *FOXP1* variants is recommended as an exclusion test when diagnosing PTI/NEHI.[35,36]

Echocardiography should be performed at the time of initial chILD diagnosis and systematically as a part of severity assessment.[20] In our study, it was carried out in almost all patients, demonstrating uniformity of practice across participating countries. Of note, consistent with previous studies, the patients demonstrated only mild cardiac defects, and none had pulmonary hypertension.[3,16,18] The role of flexible bronchoscopy with bronchoalveolar lavage in PTI/NEHI is not well defined. In children with PTI/NEHI who underwent

Figure 2 – *A-C, Bar graphs showing percentage of patients specific symptoms (A) and undergoing the listed investigations (B, C). Comparison among countries with at least 10 reported cases. IPFT = infant pulmonary function test; LUS = lung ultrasound; PSG = polysomnography.* [a]χ^2.

bronchoscopy, no significant anatomic abnormalities or characteristic signs in bronchoalveolar lavage cellularity were found.[37] In the present cohort, bronchoscopy was performed in approximately one-half of the patients, with considerable variation among countries. Some centers performed it almost universally, whereas others

TABLE 5 Comparisons Between Countries With ≥ 10 Cases Reported

Variable	Poland (n = 137)	Germany (n = 62)	France (n = 53)	Spain (n = 25)	United Kingdom (n = 21)	Israel (n = 15)	Slovenia (n = 12)	Denmark (n = 10)	Turkey (n = 10)	*P* Value[a]
Age at diagnosis, mo	10 (7-13)	11 (6-13)	11 (7-35)	6 (5-9)	9 (5-11)	7 (4-11)	6.5 (6-8)	9.5 (7-12)	7 (4-16)	.0089
Diagnostic delay, mo	4 (2-6)	5 (3-9)	6 (3-31)	4 (3-7)	6 (2-9)	2 (1-6)	2 (1-4)	6.5 (4-10)	4.5 (3-8)	.0056

Data are presented as median (interquartile range).
[a]Kruskall-Wallis test.

did so only occasionally. Because the usefulness of bronchoscopy in PTI/NEHI has not yet been demonstrated, it is worth considering whether this examination should remain part of the diagnostic approach or should be reserved for patients who have additional relevant indications like infections or tracheobronchial abnormalities. Our study confirmed the limited availability and experience in performing infant pulmonary function testing. Breuer et al[24] demonstrated that infants with PTI/NEHI have markedly increased functional residual capacity and that infant pulmonary function testing may be used in diagnostic evaluation. The usefulness of pulmonary function testing in PTI/NEHI requires confirmation in larger patient cohorts.

In the study by Liptzin et al,[6] several comorbidities were identified. These include GERD, OSA, and immunologic abnormalities. The number of procedures performed to assess these comorbidities varied considerably among the countries participating in our study. Monitoring of pH was performed in just > 30% of the cohort. Notably, 42.1% of these patients met the criteria for a GERD diagnosis. According to previous publications, 28.3% to 51.0% of patients with PTI/NEHI may have GERD, and one-third may experience aspiration.[6,22] GERD in PTI/NEHI is likely to be a secondary phenomenon. Pulmonary hyperinflation can cause diaphragm dysfunction and bronchoconstriction, altering the pressure gradient between the thorax and abdomen and leading to gastroesophageal reflux.[21] Previous studies have indicated that sleep-related breathing disorders are more prevalent among patients with PTI /NEHI than in the general population.[21,38] In our data, the number of reported sleep studies was relatively low, with important differences among countries. The results indicate that nearly 70% of the children tested had a diagnosis of OSA.[39] It is possible that this result has been affected by selection bias, because children with OSA symptoms may have been examined more frequently. Because of this high prevalence of GERD and OSA, a well-designed study is required to confirm these findings and to establish optimal treatment strategies. When symptoms suggest the coexistence of these conditions, pH monitoring or polysomnography should be conducted. Most patients underwent diagnostic evaluations for immune disorders, with no significant differences observed among countries. However, the extent of the tests performed varied considerably. In some patients, only neutrophil and lymphocyte counts or immunoglobulin levels were assessed, whereas in others,

evaluations included IgG subclasses, complement component levels, and oxidative burst activity. Similar to the findings of Liptzin et al,[6] the abnormalities detected were mild. However, because of the variability in the extent of testing, it is difficult to draw definitive conclusions. Future prospective studies would help to define the spectrum of immunologic abnormalities in PTI/NEHI better.

Study Limitations

Some limitations of this study should be noted. The number of patients included from different countries was not proportional to the size of their populations, which may have affected the representativeness of the data. The patients with PTI/NEHI were contributed by clinicians who voluntarily participated in the study, which might have led to some patients being underrepresented. The uneven distribution of patients also could be influenced by factors such as ethnicity or local environmental conditions, although these aspects remain unclear. Differences in health care system organization across countries also may have played a role. For instance, in France, chILD care centers are distributed widely among the RespiRare centers, whereas in other countries, care is more centralized.

Because this was a retrospective study, some data were missing. For example, the NEHI Clinical Score could not be calculated for all patients because of missing components. Additionally, some patients included in this cohort received a diagnosis in the early 2000s, a time when NEHI was not yet recognized fully, potentially leading to delayed or missed diagnoses. Despite these limitations, the study managed to collect the largest recorded cohort of patients with PTI/NEHI to our knowledge, enabling a comparison of diagnostic approaches among countries.

Interpretation

The present study indicated that in all participating countries, the diagnosis of PTI/NEHI primarily is based on characteristic clinical symptoms and radiographic findings on chest HRCT imaging. The role of lung biopsy has declined over time. Significant differences exist among countries in the number and type of additional tests used in the diagnostic process. These findings underscore the need to establish uniform recommendations outlining the basic minimum diagnostic requirements to avoid the use of tests with limited diagnostic value. Given the rarity of PTI/NEHI and the challenges associated with conducting prospective studies, the use of a Delphi process to develop consensus-based guidelines is essential.

Funding/Support

The authors have reported to *CHEST* that no funding was received for this study.

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Author contributions: H. M. takes responsibility for the content of the manuscript, including the data and analysis. H. M., K. K., and M. Griese substantially contributed to the conception and design of the work, data acquisition and analysis, and interpretation of data for the work; drafted the work; reviewed it critically for important intellectual content; and gave final approval of the version to be published. N. N. and J. P. substantially contributed to the conception and design of the work, data acquisition and analysis, and interpretation of data for the work; reviewed the draft critically for important intellectual content; and gave final approval of the version to be published. J. L., M. K., M. Grochowska, E. S., J.-C. D., J. R., N. S., J. C., O. B., A. H., S. C.-C., M. A., F. F. B., K. G. N., S. M., A. T., M. B.-L., N. R., F. S. , P. L., A. Z., E. H., R. A., T. Ş. E., E. E., M. P., S. C., D. M., S. P., N. C., L. N., C. L., N. U., W. B., D. K., M. Gaboli, N. D. M., D. N. V., S. L. M. R., B. W., L. P., A. W., D. S., C. M., F. P., V. K., and J. A. L.-A. contributed to the conception and design of the work and data acquisition, revised the draft, and gave final approval for publication.

Declaration of generative AI and AI-assisted technologies in the writing process: ChatGPT was used to assist with grammar and style checks, followed by a manual review and final proofreading of the text.

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