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Growth Trajectories and Oxygen Use in Neuroendocrine Cell Hyperplasia of Infancy

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Abstract

Rationale—Neuroendocrine cell hyperplasia of infancy (NEHI) typically presents in infancy with tachypnea, retractions, and hypoxemia. Some infants have failure to thrive, yet the frequency of this and other non-respiratory phenotypic features have not been delineated. While gradual improvement occurs, the clinical course is variable and the duration of supplemental oxygen requirement has not been defined.

Objectives—Our objective was to identify factors in NEHI that may drive differences in clinical course. We hypothesized that failure to thrive would be associated with greater duration of supplemental oxygen use.

Methods—Children with NEHI were identified as a nested retrospective cohort within an ongoing observational prospective study. An electronic questionnaire evaluating health status was distributed to the parents/guardians. Clinical data were obtained via chart review and parent interview.

Results—Of 42 children, 74% had a diagnosis of failure to thrive during their clinical course. Time to event analysis demonstrated that 50% discontinued daytime and nighttime oxygen at 32

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Author contributions:

Dr. Young had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Nevel: contributed to the study inception, data acquisition and analysis, drafted the manuscript, provided critical input into the final version of the manuscript, and approved the final version of the manuscript.

Ms. Garnett: contributed to the data acquisition and analysis, provided critical input into the final version of the manuscript, and approved the final version of the manuscript.

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Dr. Young: contributed to study inception and data acquisition and analysis, drafted the manuscript, provided critical input and helped revise the final version of the manuscript, and approved the final version of the manuscript.

and 87.5 months after initiation, respectively. Diagnosis of failure to thrive was associated with longer continuous oxygen supplementation, $p=0.03$. Additional parental concerns identified through the electronic questionnaire (response rate 95%) included developmental delays (38%), multiple hospitalizations, and delays in diagnosis.

Conclusions—NEHI is associated with substantial respiratory and extra-pulmonary morbidity. Failure to thrive may be associated with greater respiratory morbidity, though further studies are required to define this interaction. Determining the association of these comorbidities and respiratory course in NEHI may enable development of strategies to improve these modifiable factors and potentially pulmonary outcomes.

MeSH key words

Neuroendocrine cell hyperplasia of infancy; childhood interstitial lung disease; child development; failure to thrive; oxygen inhalation therapy

INTRODUCTION

Neuroendocrine cell hyperplasia of infancy (NEHI) is a form of childhood interstitial lung disease (ILD) that presents with insidious onset of tachypnea, retractions, and hypoxemia in infants.¹⁻⁴ The chest computed tomography (CT) findings, pulmonary function test patterns, and lung biopsy diagnostic criteria for NEHI have been well defined.⁴⁻⁷ While genetic mechanisms play a role in at least some cases, identification of an underlying pathogenic trigger has remained elusive in most children. No specific treatments are available and disease management remains limited to supportive care such as supplemental oxygen. Children with NEHI improve over time, with no reported mortality, though the pace and clinical course are highly variable. Recent data indicate persistence of disease manifestations into later childhood and even adulthood in some cases, while others improve remarkably by preschool years.^{2,8-12} The factors which modify disease course and drive these variable clinical outcomes are poorly understood.

Failure to thrive is a frequent though not universal feature in children with NEHI,^{4,7,10,11} and our clinical experience is that nutritional supplementation is provided in many cases. Nutrition is fundamental in treatment of other lung diseases such as cystic fibrosis (CF), where achieving body mass index (BMI) goals are prioritized to maintain lung function over time, and higher BMI goals exist for individuals with CF compared to the rest of the population.^{13,14} However, in NEHI, it is unknown whether malnutrition contributes to and/or is a marker of pulmonary morbidity, and there are no established targets for nutritional status. Further, other than failure to thrive, extra-pulmonary morbidity has not been reported in children with NEHI. Our objective was to identify factors and comorbidities that may associate with and drive variability in the respiratory disease burden and clinical course of NEHI. Here we report the duration of oxygen use in NEHI and provide novel longitudinal data on failure to thrive in this population and its association with respiratory morbidity. Some of these data have previously been presented in abstract form.¹⁵

MATERIALS AND METHODS

Children with NEHI were enrolled in a prospective study of childhood ILD at Vanderbilt University from 2013 to 2016. This current study was performed as a nested retrospective cohort within the longitudinal study. All research was approved by the Vanderbilt Institutional Review Board, protocol #131026. Participants were recruited through the Vanderbilt Pediatric Rare Lung Disease Clinic or remotely via the Children's Interstitial Lung Disease Foundation. Study inclusion criteria were individuals 0-18 years of age with NEHI diagnosis and informed parental consent. Potential subjects were excluded if there was a lack of diagnostic confirmation or insufficient records for review.

Diagnosis was confirmed based on established clinical, radiologic, or histologic criteria.^{3,6} Parents/guardians of children with NEHI were asked to report their perspectives on the health status of their children using an exploratory electronic questionnaire to identify domains of concern. Additional clinical data were obtained via chart review and interview of parents. Growth status measures included provider diagnosis of failure to thrive, weight-for-age percentile at time of oxygen initiation, and growth trends over the first five years of life at pre-specified ages based on the American Academy of Pediatrics recommended well child checks (birth, 2 months, 4 months, 6 months, 9 months, 12 months, 18 months, 2 years, 3 years, 4 years, and 5 years). Weight-for-age and weight-for-length percentiles were determined by World Health Organization growth charts by sex for children less than age 2 years; weight-for-age and BMI percentiles were determined by Center for Disease Control and Prevention growth charts by sex for children greater than age 2 years. Subjects were included for growth analysis if they had at least three growth points documented within the first year of life.

Study data were collected and managed securely using REDCap electronic data capture tools hosted at Vanderbilt University Medical Center.¹⁶ Statistical analysis was completed with STATA[®] Statistics/Data Analysis 14.2 (from StataCorp, 2015, *Stata Statistical Software: Release 14*, College Station, Texas) and GraphPad Prism (version 7.00, GraphPad Software, La Jolla, California, USA). The primary marker for respiratory morbidity was duration in months of continuous supplemental oxygen. Secondary indicators of respiratory morbidity were duration of nighttime supplemental oxygen use and maximum home supplemental oxygen flow. Time to event analysis was completed for duration of supplemental oxygen, with log rank analysis for between group comparisons for failure to thrive status at any time during clinical course. Chi-square analysis was used for analysis of categorical data, and Student's t-tests or Mann Whitney U tests were used for analysis of continuous data. Confidence intervals (CI) are reported as 95% CI by bootstrapping technique using a seed of 1234. P value significance was set at $p < 0.05$.

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RESULTS

A total of 49 subjects with clinically reported diagnosis of NEHI were identified from within the childhood ILD prospective study as of January 1st, 2017 (Figure 1). Seven subjects were excluded from analysis for this nested retrospective cohort study per specified exclusion criteria: six due to insufficient records available for diagnostic confirmation and one over 18 years of age. Thus 42 eligible subjects remained for chart review and parent/guardian surveys.

Demographics and clinical characteristics of the study cohort are displayed in Table 1. While prior publications have reported a male predominance in NEHI,^{2,5,7} 59.5% of subjects in this study were female. The median age of subjects was 54.5 months with a range of 5-138 months at the time of data collection. Median age at diagnosis of NEHI was 8.5 months (95% CI 5.3-12.7). Parents reported that symptom onset, including poor weight gain, poor feeding, rapid breathing, or retractions, occurred at a median age of 3 months (CI 2.2-3.8). The median age at home supplemental oxygen initiation was 6 months (CI 4.8-7.2), with initial chest CT performed at a median age of 7 months (CI 5.8-8.2). A subset of the cohort (n=17, 40%) underwent lung biopsy, at a median age of 11 months (CI 6.5-15.5). Thus, collectively, these data revealed a delay in diagnosis of 5.5 months from symptom onset to NEHI diagnosis.

Because a 2010 publication prompted greater reliance on chest CT findings rather than lung biopsy for NEHI diagnosis,⁵ we examined whether the delays in NEHI diagnosis have changed over time. We found that NEHI diagnosis occurred at an older age for subjects born prior to 2010 in comparison to those born after 2010 (14.5 vs. 7 months, $p=0.02$). As symptom onset before and after 2010 were similar (median of 3 vs. 2.5 months), there was a significant difference in the delay in diagnosis if born before versus after 2010 (11.5 vs. 4.5 month delay, respectively, $p=0.004$). Of note, most subjects born prior to 2010 underwent lung biopsy, while subjects born after 2010 were less likely to undergo lung biopsy (10/12 (83%) vs. 7/30 (23%) of subjects, $p<0.001$).

Assessment of burden of disease for families of children with NEHI was evaluated with a questionnaire asking parents / guardians to report perspectives on various aspects of the health status of their child with NEHI (Supplemental Figure 1). Frequency of hospitalization was one indication of burden of disease for affected families, as 87% of children had at least one hospitalization and 36% of children had four or more hospitalization events reported during the first year of life. The frequency of hospitalization was similar for children born before and after 2010. With respect to medication and treatment burden, during the prior year, 60% of participants were treated with inhaled beta-agonists, 38% with inhaled corticosteroids, 34% with oral glucocorticoids, and 31% received medications for gastroesophageal reflux. Chart review and parent phone interviews were performed to verify data from the electronic questionnaire (Table 2). Developmental delays, including domains of speech and language development, fine motor skills, gross motor skills, and sensory processing, were documented in 38% of subjects. Interventions included speech feeding therapy for 37%, speech language therapy for 24%, physical therapy for 17%, and occupational therapy for 17%.

In the questionnaire, 65% of parents reported they had been concerned about their child's growth. 74% of this cohort had a diagnosis of failure to thrive documented by a medical provider at some time during their clinical course. 13 (31%) subjects underwent g-tube placement, at a median age of 9 months (CI 3.6-14.4 months). We requested historical growth records from primary care and subspecialty providers to validate and further investigate these findings; acceptable longitudinal weight data were available for n=33 (79%) of subjects and longitudinal BMI and weight-for-length data were available for n=26 (62%). Among subjects with available serial growth data, 77% had failure to thrive based on decline in weight-for-length / BMI over two major growth curves or falling below the 3rd percentile for age and sex. Examination of the trajectories for mean weight-for-length / BMI percentile demonstrated an initial decline in percentiles with nadir occurring around 4 months of age followed by a recovery phase (Figure 2A). The weight-for-age percentile trajectories (Figure 2B) appeared similar to the BMI trajectories, with a prominent decline occurring during the first few months of life and subsequent recovery of percentiles. For some subjects, the improvement in growth velocity appeared to occur in temporal association with initiation of supplemental oxygen. However, available data did not allow us to conclude whether supplemental oxygen or nutritional supplementation, including via g-tube placement, directly facilitated improved growth, as sample size was inadequate to use oxygen initiation or g-tube placement as time-varying covariates.

Supplemental oxygen requirement is a primary aspect of respiratory morbidity in NEHI, and the majority of subjects (97.6%) required some amount of home supplemental oxygen during their clinical course. The median maximum oxygen flow rate required was 1 liter per minute (LPM) (95% CI, 0.25-3.5 LPM). 50% of NEHI subjects who required continuous supplemental oxygen had discontinued daytime oxygen by 32 months after oxygen initiation (Figure 3A). Nighttime supplemental oxygen use was more prolonged, with discontinuation for 50% of subjects not occurring until more than 7 years after oxygen initiation (87.5 months) (Figure 3B). Alternatively, when analyzed for duration of oxygen use to date, the median durations of continuous and nighttime supplemental oxygen use were 30.1 months (95% CI, 21.1 – 39.2) and 41 months (95% CI, 35.4 – 55.2), respectively (Table 2).

To evaluate for a potential correlation between growth failure and respiratory morbidity, the duration of continuous supplemental oxygen was defined as the primary endpoint. A diagnosis of failure to thrive at any time during clinical course was associated with longer duration of continuous supplemental oxygen use (Figure 4, log rank test, p=0.03). Secondary outcomes including nighttime oxygen duration and maximum home oxygen flow rate were not associated with a diagnosis of failure to thrive. Additionally, there was no significant association between g-tube placement or developmental delays in any domain and the measures of pulmonary morbidity (i.e., continuous oxygen duration, nighttime oxygen duration, or maximum home oxygen flow).

DISCUSSION

In the largest reported cohort of children with NEHI, this study provides novel insights into natural history of this rare disease, including longitudinal growth trajectories and duration of supplemental oxygen use. Though a common question asked by parents, the duration of

oxygen supplementation in NEHI has not been comprehensively evaluated. We found that 50% of subjects had discontinued supplemental daytime oxygen after 32 months and nighttime oxygen at over 80 months. Although clinical improvement occurred over time, disease burden was substantial, including frequent hospitalizations, failure to thrive, and developmental delays. Our data also indicate an association between the duration of oxygen supplementation use and failure to thrive.

Failure to thrive has been reported to be common in childhood ILD,^{3,17,18} and the approximately 75% rate of failure to thrive diagnosis in our study is consistent with prevalence rates of failure to thrive in smaller NEHI cohorts.^{2,4,5,11,18,19} Longitudinal trajectories of weight-for-length / BMI percentile have not been previously analyzed in NEHI. We observed that a decline in weight-for-length percentiles occurred within the first few months of life, with nadir around 4 months of age followed by relative percentile recovery. Interestingly, the improvement in growth trajectory for the cohort occurred prior to the median age for g-tube placement among the subset (31%) receiving that intervention. Further, several subjects exhibited persistently low weight-for-age percentiles and lack of catch up growth to date despite nutritional supplementation via g-tube (Supplemental Figure 2).

Nutrition and growth have been extensively studied in other pediatric pulmonary conditions, including CF and bronchopulmonary dysplasia. Specific to CF, it has been repeatedly demonstrated that lung function correlates with BMI percentiles, and nutritional optimization is highly emphasized in management.^{20,21} Unlike CF, children with NEHI do not have malabsorption or chronic infectious processes to account for growth failure; rather, the prominent tachypnea associated with NEHI in infants is hypothesized to increase resting energy expenditure. We found that children with failure to thrive had a longer duration of continuous supplemental oxygen requirement. The nature of this interaction is unclear. While poor growth and nutritional status may directly affect the respiratory course, it is possible that parents/providers may be less likely to wean oxygen if growth concerns remain. As reliable weight and length data were not available at the time of oxygen initiation for most subjects, further studies are required to define whether failure to thrive is a prognostic biomarker, as opposed to a marker for more significant respiratory disease.

Our data indicate an overall delay of 5.5 months from symptom onset to NEHI diagnosis. This delay has important implications regarding potential for unnecessary testing, hospitalizations, and other healthcare utilization during this time, as well as potential stress for families. The approach to diagnosis of NEHI has changed over time, with less reliance on lung biopsy. Instead use of specific chest CT findings in conjunction with an appropriate clinical context are now considered sufficient for NEHI diagnosis, per American Thoracic Society clinical guidelines.⁶ We found that numbers of lung biopsies and NEHI diagnostic delay have decreased in recent years. While these changes in practice patterns may indicate an improvement in both disease recognition and diagnostic practices, opportunity for ongoing improvement in diagnostic efficiency remains. Rauch et al recently reported a cohort of infants with persistent tachypnea including diagnosis of NEHI, though different case definitions were utilized.¹⁹ Several aspects of the clinical course are similar in our study and that by Rauch et al, including age at symptom onset (3 months vs. 3.5 months),

age at lung biopsy (0.92 vs. 1.2 years), and rates of failure to thrive (75% vs. 66%). Our cohort had a higher rate of oxygen supplementation and longer duration of use than that reported by Rauch et al, though direct comparisons of the cohorts are limited by differences in data reporting and study inclusion criteria.

The reported burden of disease also included frequent hospitalizations in the first year of life. Medication use within the prior year was common for both inhaled beta-agonists (60%) and inhaled / oral corticosteroids (approximately 30% each). We were surprised by the frequency of use of these medications, as a prior study on infant pulmonary function testing demonstrated a lack of bronchodilator response⁷ and airway inflammation is typically absent in NEHI lung histopathology.³ As such, it is unclear if this medication use indicates the presence of additional comorbid respiratory conditions or may represent a potentially unnecessary burden of care, and thus an opportunity for education of medical professionals about management of NEHI.

Developmental delay has not been previously reported in the NEHI population, and this study was not designed to formally evaluate developmental milestones. Therefore it was an unanticipated observation that approximately one-third of children in this cohort had developmental delays, often in several domains, as reported by parents and confirmed in the medical records. The frequency of speech, occupational, and physical therapy received by these children suggest that the prevalence of developmental delays reported by parents in the questionnaire is unlikely to be an over-estimate. It is unknown whether the etiology of the developmental delay is intrinsic to the disease process of NEHI or if it is a consequence of respiratory morbidity, failure to thrive, or frequent hospitalizations. There was no statistically significant association between the presence of developmental delays in this cohort and variables including respiratory morbidity, failure to thrive, or frequency of hospitalizations. Further, we did not identify other common contributors to developmental delay in this cohort. Specifically, only one subject had the reported *NKX2-1* mutation associated with NEHI, and only 4 subjects had history of late preterm birth (35-36 weeks gestation) without perinatal morbidity. No children with NEHI in our clinical practice have a diagnosis of hypothyroidism, though testing was not formally performed on all subjects as part of this study. Further studies are needed to compare the prevalence of these findings to other relevant age-matched control groups, to characterize the duration and severity of delays, and to evaluate the factors influencing developmental delays. Developmental assessment is not standard practice in pulmonary clinic, yet since early developmental interventions are known to improve developmental outcomes for delays in pediatric patients, ^{22–24} monitoring developmental milestones in children with NEHI may be indicated.

A limitation of this study is the retrospective study design, including that growth data were derived from chart review of records rather than protocol driven measurements. Although detailed growth data were not available for all subjects, the prevalence of failure to thrive was similar based on medical record diagnosis within the entire cohort and the subgroup with growth curve analysis, suggesting that this was likely a representative sample of the full cohort in this study. Duration of oxygen supplementation was selected as the primary endpoint for pulmonary morbidity in this study, as this is important to families and may reflect functional limitations in these subjects. Serial objective measurements such as

pulmonary function testing and overnight polysomnograms were not available for most of these young subjects and will be informative for future studies of pulmonary outcomes. Although this study represents the largest cohort to date for this rare disease, the sample size provided limited statistical strength to develop predictive tools from this data. Approximately half of subjects did not follow in our center for continuity of pulmonary care, and therefore, the diagnostic and clinical course reported here reflects more diverse clinical experiences across the NEHI population beyond practice patterns at our center.

In conclusion, this study provides new insights into disease burden, extra-pulmonary morbidity, and clinical patterns of oxygen use and growth in children with NEHI. This information regarding the clinical and diagnostic course as well as extra-pulmonary disease manifestations is useful to both providers and affected families and should inform future studies. Understanding the clinical variability in NEHI may enable the development of strategies to improve these modifiable factors and potentially improve pulmonary course in this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations List

BMI	body mass index
CI	confidence intervals
CT	computed tomography
CF	cystic fibrosis
G-tube	gastrostomy tube
ILD	interstitial lung disease
LPM	liters per minute
NEHI	Neuroendocrine cell Hyperplasia of Infancy

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Figure 1. Study Design Flow and Subject Inclusion

Abbreviations: ChILD = childhood interstitial lung disease, NEHI = neuroendocrine cell hyperplasia of infancy, BMI = body mass index

Figure 2. Growth Percentile Trajectories in NEHL, Birth – 5 Years

A. Weight-for-length / BMI percentile means in the first five years of life, with 95% confidence interval (n=26). B. Weight-for-age percentile means in the first five years of life, with 95% confidence interval (n=33). BMI = body mass index. CI = confidence interval. Weight-for-length percentile used for <2 years (World Health Organization growth charts), BMI percentile used for >2 years (Center for Disease Control and Prevention growth charts)

Figure 3. Duration of Supplemental Oxygen Use

A. Kaplan-Meier analysis with 95% confidence intervals. 50% of subjects who required continuous supplemental oxygen had weaned off daytime oxygen 32 months after initiation.

B. Kaplan-Meier analysis with 95% confidence intervals. 50% of subjects who required nighttime supplemental oxygen had weaned off supplemental oxygen 87.5 months after initiation.

Figure 4. Duration of Continuous Supplemental Oxygen Use based on Failure to Thrive. Data show duration of continuous supplemental oxygen use for NEHI subjects with failure to thrive (FTT) in comparison to children with NEHI without FTT (log rank test, $p = 0.03$).

Table 1

Subject Demographics and Clinical Characteristics

Sex Male Female	40.5% 59.5%
Ethnicity Caucasian, non-Hispanic ethnicity	100%
Current age in months (median, range)	54.5 (5 – 138)
NEHI diagnosis, age in months (median, 95% CI)	8.5 (5.3 – 12.7)
Symptoms onset, age in months (median, 95% CI)	3 (2.2 – 3.8)
Supplemental oxygen initiation, age in months (median, 95% CI)	6 (4.8 – 7.2)
Initial chest CT, age in months (median, 95% CI)	7 (5.8 – 8.2)
Lung biopsy, age in months, n=17 (median, 95% CI)	11 (6.5 – 15.5)

Table 2**Respiratory, Growth, and Developmental Morbidity in NEHI**

Respiratory Morbidity		N
Home supplemental oxygen use (ever)	97.6%	42
Maximum home supplemental oxygen use (median LPM, 95% CI)	1 (0.25 – 3.5)	41
Supplemental oxygen initiation, age in months (median, 95% CI)	6 (4.8 – 7.2)	41
Continuous oxygen supplementation duration, in months (median, 95% CI) *	30.1 (21.1 – 39.2)	33
Nighttime oxygen supplementation duration, in months (median, 95% CI) *	41 (35.4 – 55.2)	41
Growth Morbidity		
Failure to thrive diagnosis (ever)	74%	42
Weight percentile at oxygen initiation (median, 95% CI)	12 (3.4-20.6)	35
G-tube or GJ-tube (ever)	31%	42
G-tube placement, age in months (median, 95% CI)	9 (3.6 – 14.4)	13
Developmental Morbidity		
Developmental Delay (ever)	38.1%	42
Speech Feeding Therapy	36.8%	38
Speech Language Therapy	23.8%	42
Physical Therapy	17.1%	41
Occupational Therapy	16.7%	42

N = total number of subjects for whom each data element is available.

* Note that median duration reflects duration at time of study performance and is ongoing in many young subjects (as displayed in Figure 3).

Abbreviations: LPM = liters per minute, 95% CI = 95% confidence interval with bootstrapping (seed 1234), G-tube = gastrostomy tube, GJ-tube = gastrojejunostomy tube