Western States Conference

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1st year pediatric pulmonary fellow
5/25/11
History of present illness

• 11 month old male referred to pulmonary clinic by PCP
• Chief complaint: hypoxemia and failure to thrive
• Hospitalized at age 3 months for H1N1 infection and pneumonia
• Sent home on ¼ L O2 which the family discontinued several months prior to presentation
Review of systems

- **CONSTITUTIONAL:**
  - +failure to thrive
  - no fevers

- **HEENT:**
  - +snoring
  - no chronic nasal congestion, recurrent otitis media, or stridor

- **RESP:**
  - +coughing and choking with feeding, persistent retractions and tachypnea
  - no chronic cough or wheeze

- **CARDIAC:**
  - +PFO otherwise normal echo
  - no cyanosis

- **GI:**
  - +constipation and reflux
  - no steatorrhea

- **SKIN:**
  - no rashes, eczema, or birthmarks

- **NEURO:**
  - normal development, very active
Past medical/family/social histories

- Birth: term, born in CO, pregnancy uncomplicated, in nursery x 4 days for “swollen head”, normal NBS
- Surgeries: none
- Family hx: negative for respiratory problems, + polycystic kidney disease
- Medications: none
- Allergies: none
- Immunizations up to date
- Social: lives with parents, no daycare, pets, or smoke exposure, no travel outside CO, no TB exposures
Physical exam

- BP 108/66 | Pulse 143 | Temp 98.1 (Tympanic) | Ht 71 cm (12%ile) | Wt 7.1 kg (0.06%ile) | SaO2 84% on room air, 88% on repeat
- GEN: happy and playful. Thin with some retractions and a slightly protuberant belly.
- HEENT: TMs normal, no rhinorrhea, oral mucosa moist and normal voice; no stridor
- NECK: no lymphadenopathy, trachea midline
- Lungs: normal I:E ratio, + crackles RML and LUL
- CV: regular rate & rhythm, normal S1, normal S2 without augmented P2 and no murmur
- ABD: soft, nontender, nondistended and without organomegaly or mass
- Skin: well perfused, no rashes
- EXT: no cyanosis, clubbing, or edema
- Neuro: grossly nonfocal, normal tone, and appropriate for age
Initial chest x-ray, age 11 months
Differential Diagnosis
Differential Diagnosis

- Cystic fibrosis
- Chronic aspiration
- Reflux
- Pulmonary hypertension
- Congenital heart disease
- Interstitial lung disease
- Primary ciliary dyskinesia
- Tracheoesophageal fistula
- AVM or other shunt
Next steps

• Started on 1/4L O2
• Further work up arranged:
  – Bronchoscopy
  – High resolution chest CT
  – Modified barium swallow study
  – Echo
  – Sweat test
Work up

• Bronchoscopy:
  – Purulent endobronchial secretions in left bronchi, otherwise normal anatomy
  – BAL from LLL:
    • 271 WBC (4segs/16lymphs/6monos/71alv macrophages)
    • 32 RBCs
    • Lipid index < 10, iron index < 10
  – Cultures negative for bacteria, fungus, mycoplasma, mycobacteria, chlamydia
  – Viral DFA and PCR negative
Work up

- Sweat test and CF genotype: negative
- Modified barium swallow:
  - Deep penetration and silent aspiration with thin liquids but limited study
  - Follow up study normal without aspiration
- Immunoglobulins: normal
  - IgA 9, IgG 440, IgM 46, IgE 14
High resolution chest CT
Echo

- Normal segmental cardiac anatomy
- Trivial tricuspid regurgitation, inadequate to estimate RV pressure
- Minimal interventricular septal flattening
- Small patent foramen ovale with left-to-right shunt
- Left aortic arch with aberrant right subclavian artery
- Normal biventricular dimension and systolic function.
Next steps
Next steps

• Presumptive diagnosis: neuroendocrine cell hyperplasia of infancy (NEHI)

• Management plan:
  – Continued on 1/2L O2
  – Pediasure supplementation
  – Further diagnostic work up with infant PFTs
Neuroendocrine cell hyperplasia of infancy (NEHI)

- Initially described as “persistent tachypnea of infancy”
- Mean age of onset of symptoms 3.8 months (range 0-11 months)
- Presenting symptoms: persistent retractions, tachypnea, hypoxemia, crackles on chest exam
- Rare: wheezing, prominent cough, neonatal respiratory distress, prematurity
- CXR: hyperexpansion, increased interstitial markings
- HRCT: increased segmental ground-glass densities
- Lung biopsy: neuroendocrine cell hyperplasia, otherwise nonspecific

Deterding et al 2005
NEHI: pathogenesis

• Pulmonary neuroendocrine cells (NEC)
  – Granulated epithelial cells found in the conducting airways and as neuroepithelial bodies in lung parenchyma
  – Play a role in regulating fetal lung development
  – Levels of cells peak in mid gestation, decline rapidly after neonatal period
  – Produce bombesin-like peptide, serotonin, and calcitonin that play roles in bronchoconstriction, vasoactivity, epithelial differentiation, and smooth muscle alteration

Deterding et al 2005
NEHI: pathology

- Increased proportion of neuroendocrine cells in the distal airways by bombesin immunohistochemistry
- NEC hyperplasia seen in lung injury and other lung diseases:
  - cystic fibrosis
  - bronchopulmonary dysplasia
  - sudden infant death syndrome
  - adult ILD: diffuse idiopathic pulmonary NEC hyperplasia
- NEHI characterized by otherwise near-normal lung histology and absent or minor airway injury

Young et al 2011
NEHI: pathogenesis

• Remaining questions:
  – Pathogenesis of NEC hyperplasia in NEHI
  – Relationship between NEC hyperplasia and hypoxemia and small airways obstruction seen in NEHI (Deterding et al 2005)
    • Correlation between degree of NEC hyperplasia and degree of small airways obstruction (Young et al 2011)

• Case description of 4 families with multiple siblings diagnosed with NEHI: possible genetic and/or environmental factors (Popler et al 2010)
Infant lung biopsy classification

Deutsch et al 2007
NEHI: diagnosis

- Gold standard = lung biopsy
- “NEHI syndrome”- diagnosis based on characteristic clinical and imaging findings rather than on lung biopsy
- Characteristic chest CT and infant PFT findings may decrease need for lung biopsy for diagnosis
Role of chest CT in NEHI diagnosis

- Best imaging of lung parenchyma: high resolution protocol with inspiratory and expiratory imaging
- Most common finding: ground-glass opacification in RML and lingula
- Second most common finding: mosaic air trapping
- Sensitivity and specificity of HRCT in NEHI diagnosis: 78% and 100%

Brody et al 2010
Role of infant PFTs in NEHI diagnosis

• Retrospective study of 57 infant PFTs
  – 15 patients with NEHI
  – 22 patients with NEHI syndrome
  – 20 disease control patients

• NEHI and NEHI syndrome patients
  – Significantly increased airflow obstruction and air trapping compared to disease controls

Kerby et al 2011
Our patient: Infant PFTs

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Testing comments.
Good study. FRCpleth, Inflated forced flows, tidal breathing and VmaxFRC met reserchar criteria. 2 quality ERV's. No acceptable compliance. Testing stopped due to signs of waking and ECHO to follow. Sedation with 850mg (97mg.kg) Chloral Hydrate. Testing on 40% with SaO2 = 95-98%. EtCO2 = 39-43mmHg. SaO2 fell into the low 80'S when O2 fell off while patient trying to fall asleep.

Interpretation
Good study. Possible early small airway obstruction. Air trapping by lung volume. Tachypnea on tidal breathing. No previous studies.
NEHI: clinical course

• Treatment: supplemental O2, nutritional support
• No sustained response to bronchodilators and glucocorticoids
• Follow up of 12 patients at age ~ 5 years:
  – Most patients discontinue O2 between 2-4 years of age
  – No known mortality
  – Spirometry: normal in 6/12 patients, mild obstruction in 1/12, evidence of air trapping in 2/6 with normal PFTs
  – 10/12 patients with occasional respiratory dysfunction (mild exercise intolerance, intermittent tachypnea, wheezing, or crackles)

Deterding et al 2005
Long term outcomes

- Retrospective review of cases at 2 pediatric centers of patients diagnosed with NEHI with persistent symptoms past 7 years of age
  - 10 patients identified
  - 7/10 male
  - Supplemental O2 discontinued at mean 7.3 years of age (range 3-18)
  - 9/10 had dyspnea with exercise
  - 8/10 had hyperinflation on lung volumes
  - 2/10 had obstruction on spirometry
  - 2/10 had normal PFTs
Our patient

- Maintained on 1/2L O2 NC
- Has reached 6%ile for weight and 12%ile for height with O2 and pediasure supplementation
Questions
Acknowledgements

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References