Update on ChILD

R. Paul Guillerman, MD
Associate Professor
Department of Pediatric Radiology
Objectives

- Review recent advances in the imaging of childhood interstitial lung disease (ChILD)
  - Diseases under-recognized, but highly morbid
  - Disease understanding rapidly evolving
  - Characteristic clinical and radiographic features
Imaging Technique for ChILD

- HRCT (high-resolution chest CT)
  - High spatial resolution reconstruction
  - Non-contiguous axial thin (1 mm) slices
  - Inspiratory and expiratory series
Imaging Technique for ChILD

- HRCT (high-resolution chest CT)
  - High spatial resolution reconstruction
  - Non-contiguous axial thin (1 mm) slices
  - Inspiratory and expiratory series
Imaging Technique for ChILD

- HRCT (high-resolution chest CT)
  - High spatial resolution reconstruction
  - Volumetric multidetector CT (MDCT)
  - Inspiratory series, optional expiratory series
CT Scan Technique

- Image quality and radiation dose similar
CT Scan Technique

- Expiratory views only valuable for certain disorders
Interstitial Lung Disease Classification

- Prevalent diseases in adults uncommon in children
- Several under-recognized diseases unique to childhood
NEHI - Never Ever Heard of It
Children Are Not Little Adults

Diffuse Lung Disease in Young Children
Application of a Novel Classification Scheme

Infants Are Not Little Children

Diffuse Lung Disease in Young Children
Application of a Novel Classification Scheme


Deutsch Am J Respir Crit Care Med 2007;176:1120-1128
Childhood Diffuse Lung Disease Classification

Disorders of Infancy
- Diffuse developmental disorders
- Alveolar growth abnormalities
- Specific conditions of undefined etiology - NEHI, PIG
- Surfactant dysfunction disorders
- Masquerading disorders

Disorders related to systemic disease

Disorders of the normal host (immune intact)

Disorders of the immunocompromised host
Childhood Diffuse Lung Disease Classification

Disorders of Infancy
- Diffuse developmental disorders
- Alveolar growth abnormalities
- Specific conditions of undefined etiology - NEHI, PIG

Disorders related to systemic disease

Disorders of the normal host (immune intact)

Disorders of the immunocompromised host

Surfactant dysfunction disorders

Masquerading disorders
Neuroendocrine Cell Hyperplasia of Infancy (NEHI)

- Hyperplasia of airway neuroendocrine cells
- Presents in infancy with persistent tachypnea, hypoxemia, and failure to thrive

Bombesin stain
NEHI
Highly Specific CT Findings

- Diffuse air trapping
  - Markedly elevated FRC and RV
NEHI
Highly Specific CT Findings

- Geographic ground-glass opacities
  - Especially RML, lingula, paramediastinal
What Do The CT Findings Represent?

- Unknown
NEHI

What Do The CT Findings Represent?

- Neuroendocrine cell number
  - No correlation with CT appearance of region biopsied
NEHI

What Do The CT Findings Represent?

- Neuroendocrine cell number
  - Also elevated in other types of ChILD
NEHI

What Do The CT Findings Represent?

- Neuroendocrine cell number
  - Decreases with age
  - May be marker of lung immaturity rather than causal
NEHI
“Atypical” Findings Increasingly Noted
Clinical Course

- Clinical and radiographic improvement, especially after two years of age
- Air trapping and exercise intolerance may persist into adolescence
- May develop non-atopic asthma
Childhood Diffuse Lung Disease Classification

**Disorders of Infancy**
- Diffuse developmental disorders
- Alveolar growth abnormalities
- Specific conditions of undefined etiology - NEHI, PIG
- Surfactant dysfunction disorders
- Masquerading disorders

**Developmental disorders**

**Disorders of the normal host (immune intact)**

**Disorders related to systemic disease**

**Disorders of the immunocompromised host**
Alveolar Growth Abnormalities

- Arrest at saccular stage of lung development

Normal term infant  Alveolar growth abnormality
Alveolar Growth Abnormalities

- Fewer, larger alveoli in simplified pulmonary lobules resembling “emphysema”

Normal term infant  Alveolar growth abnormality
Alveolar Growth Abnormalities
Characteristic Radiographic Findings

- Distorted pulmonary lobules
- Thick perilobular opacities
- Hyperlucent “cysts”
Alveolar Growth Abnormalities
Characteristic Radiographic Findings

- Enlarged simplified alveoli
- Hypoxic vasoconstriction
- Diminished vascular bed

→ Hyperlucency
Alveolar Growth Abnormalities
Characteristic Radiographic Findings

- Hyperlucency correlates with clinical severity
Alveolar Growth Abnormalities

- Most common chronic diffuse lung disease of infancy
- Most often associated with bronchopulmonary dysplasia (BPD) of prematurity

Other associations
- Wilson-Mikity syndrome
- Pulmonary hypoplasia
- Congenital cardiovascular disease
- Certain genetic disorders
- ? CMV infection
5-month-old former 32-week low birth weight premie with tachypnea
Minimal initial oxygen supplementation and no mechanical ventilation
Wilson-Mikity Syndrome
Alveolar Growth Abnormality
4-month-old with history of left congenital diaphragmatic hernia
Pulmonary Hypoplasia
Alveolar Growth Abnormality
7-year-old former 25-week premie with pulmonary HTN and left upper PV atresia
7-year-old former 25-week premie with pulmonary HTN and left upper PV atresia
Focal Alveolar Growth Abnormality
Full-term neonatal girl with respiratory distress

2 weeks of age

4 months of age
Progression to respiratory failure requiring lung transplantation

Inspiratory

Expiratory
Severe multilobar “emphysema”
Alveolar Growth Abnormality
Filamin A (FLNA) Gene Mutation
Alveolar Growth Abnormality
Filamin A (FLNA) Gene Mutation

- Filamin A (FLNA) gene
  - X-linked
  - Encodes an actin-binding, cytoskeletal scaffolding protein
  - Filamin A protein involved in connective tissue integrity, cardiovascular development and neuronal migration
Airway malacia in 6-month-old girl with *FLNA* mutation
Periventricular nodular heterotopia and aortic ectasia child with *FLNA* mutation
Alveolar Growth Disorder Associated with FLNA Mutations

- Additional clues include nystagmus, joint hypermobility
- Progressive respiratory insufficiency in infancy requiring lung transplant for survival
- Recognition on imaging is important to guide genetic testing and referral for lung transplant
- At risk for aneurysm rupture if survive infancy
Childhood Diffuse Lung Disease Classification

Disorders of Infancy
- Diffuse developmental disorders
- Alveolar growth abnormalities
- Specific conditions of undefined etiology - NEHI, PIG
- Surfactant dysfunction disorders
- Masquerading disorders

Disorders related to systemic disease

Disorders of the normal host (immune intact)

Disorders of the immunocompromised host
4-month-old full-term infant with respiratory failure

- Diffuse air space opacity, resembling RDS of prematurity
Surfactant Dysfunction Disorder
*ABCA3* Gene Mutations

- Diffuse air space opacity, resembling RDS of prematurity
10-year-old girl with chronic cough and shortness of breath

- Patchy ground glass opacities, cysts
Surfactant Dysfunction Disorder
ABCA3 Gene Mutations

- Patchy ground glass opacities, cysts
Surfactant Dysfunction Disorders

Gene Defect

- **ABCA3** (ATP-binding cassette subfamily A member 3)
- **SP-C** (surfactant protein C)
- **SP-B** (surfactant protein B)
- **NKX2-1/TTF-1** (NK2 homeobox/thyroid transcription factor 1)
- **SLC7A7** (solute carrier family 7 subfamily A isoform 7)
- **NPC2** (Niemann-Pick type 2C)
- **GM-CSF-R** (granulocyte monocyte-colony stimulating factor-receptor)

Pathology

- Pulmonary alveolar proteinosis (PAP)
- Chronic pneumonitis of infancy (CPI)
- Desquamative interstitial pneumonia (DIP)
- Nonspecific interstitial pneumonia (NSIP)
Surfactant Dysfunction Disorders
Radiographic Findings, Clinical Course

- Variable
  - Acute severe respiratory distress syndrome (RDS) in term neonates
  - Chronic diffuse lung disease in children and adolescents
Surfactant Dysfunction Disorder

**ABCA3 Gene Mutations**

- Most common heritable cause of surfactant dysfunction

- Disease-causing homozygous or compound heterozygous bi-allelic autosomal recessive *ABCA3* mutations

- 1/3,100 people of European descent (similar to CF)
34-week premie with prolonged RDS

Newborn

5-weeks-old
Clinical improvement later in infancy

5-weeks-old

12-months-old
Mono-allelic p.E292V ABCA3 mutation

5-weeks-old

12-months-old
**Surfactant Dysfunction Disorder**

**ABCA3 Gene Mutations**

- *ABCA3* mutations present in 3-4% of infants of European descent
- Mono-allelic *ABCA3* mutation carriers overrepresented in infants > 33 weeks of gestational age with RDS
- Single *ABCA3* mutation confers an 11% risk of non-lethal RDS in late preterm and term infants
13-month-old with congenital hypothyroidism, hypotonia, recurrent infections and hypoxemia
“Brain-Thyroid-Lung” Syndrome
NKX2-1/TTF-1 Gene Mutation
“Brain-Thyroid-Lung” Syndrome

NKX2-1/TTF-1 Gene Mutation

- **NKX2-1/TTF-1**
  - Expressed in the forebrain, thyroid and lung
  - Plays role in surfactant function, alveolarization and innate immunity
  - Sporadic or inherited autosomal dominant mutations or deletions lead to disease
“Brain-Thyroid-Lung” Syndrome

NKX2-1/TTF-1 Gene Mutation

- Maldeveloped basal ganglia in 100% - chorea, hypotonia
- Thyroid hypoplasia, hemiagenesis or athyreosis in 45%
- Severe neonatal RDS in 3/4
- Recurrent pneumonia in 1/2
- Chronic ChILD in 1/5
4-year-old with dyspnea, anemia and elevated p-ANCA
Pulmonary Capillaritis
Pulmonary Capillaritis

- Necrotitizing vasculitis of microscopic alveolar interstitial vessels
- Disruption of vessels results in pulmonary hemorrhage
Pulmonary Capillaritis

- Associated with anti-neutrophil cytoplasmic antibodies (ANCA)
- May also affect other organs, especially the kidneys
- Most have anemia and dyspnea, but not hemoptysis
- Likely accounts for many cases misdiagnosed as idiopathic pulmonary hemosiderosis
Pulmonary Capillaritis

- Requires aggressive prolonged immunosuppressants
- CT useful in monitoring treatment response
Update on ChILD Summary

- Encompasses both common and rare diseases
- Under-recognized and highly morbid
- Suspect especially in term/near-term infants with severe respiratory distress
- Some forms have very characteristic clinical and radiologic features