Pulmonary Complications of
Down Syndrome

*Putting the Puzzle Together*

Sherri Katz, MD, CM, FRCPC
Pediatric Respilologist
Children's Hospital of Eastern Ontario
University of Ottawa

Objectives

1) To identify the pulmonary complications Down Syndrome

2) To develop a comprehensive approach to diagnosis and treatment of pulmonary complications in Down Syndrome

Pieces of the Puzzle

- Structural abnormalities
- Pulmonary Hypertension
- Lower Respiratory Tract Infections
- GERD/Aspiration
- Sleep-disordered breathing
Case

• 6 y.o. ♦, Down syndrome, previous AVSD repair
• Lingering cough for 3 weeks following URTI, fever, respiratory distress
• Snores at night, increasingly restless sleep, daytime fatigue, poor concentration at school
• On exam: O₂ sat 93% in R/A, RR 30, mild indrawing, crackles RML
• CXR: RML infiltrate, subpleural cysts, normal heart size

Questions

• What is wrong with this child?
• Is it related to Down Syndrome?
• Is there more than 1 problem?
• How do I diagnose the problem?
• How do I treat?

Pieces of the Puzzle

Structural abnormalities

Lower Respiratory Tract Infections

Pulmonary Hypertension

GERD/Aspiration

Sleep-disordered breathing
Structural Abnormalities

**Mid-facial**
- Short nasal passages
- Small oropharynx
- Jaw hypoplasia
- Macroglossia
  - Not true macroglossia
  - Relatively large tongue for size of bony confines of oral cavity
- Laryngomalacia

**Upper Airway**
- Reduced upper airway size is due to soft tissue crowding within a smaller mid and lower face skeleton
- Adenoid & tonsil volume is smaller than controls (in those with no OSA Sx)
  > Uong, AJRCCM, 2001

**Upper Airway & Chest Wall**
- Choanal stenosis
- Subglottic stenosis
- Vascular rings
- ↑ incidence of 12th rib anomalies
- Pectus excavatum (18%)
- Pectus carinatum (11%)
Structural Abnormalities

Lungs

• Pulmonary hypoplasia
  » Cooney, NEJM, 1982
  – Contributes to respiratory failure
  – Study of biopsy specimens showed hypoplastic lungs more susceptible to mechanical stress from overinflation of lungs → post-op respiratory failure
  » Yamaki et al, Thorax, 1985

• Tracheal Bronchus
  – Abnormal RUL bronchus that arises directly from trachea
  » Kriss, Clinical Pediatrics, 1999
  – Prevalence 20% in small series of children with respiratory morbidity (RUL atelectasis)
  » Bertrand, Ped Pulmonol, 2003
  – Remove if bronchiectatic or stenotic bronchus with recurrent atelectasis/infection

• Subpleural cysts
  – 20% in one series
  – ↑ frequency in patients with CHD
  – Not seen on CXR
  – Symptoms not specific
  – ? May result from reduced postnatal production of peripheral small air passages and alveoli
Structural Abnormalities

Histology

- Advanced alveolar maturation
- ↓ alveolar number
- ↓ alveolar complexity secondary to deficient alveolar multiplication or acinar hypoplasia
- Contributes to pulmonary hypertension in 86%
  - Cooney, 1988
- Airway branching is reduced indicating early in utero impairment of growth
  - Shilo, Hum Pathol, 1991

Pieces of the Puzzle

Structural abnormalities

Lower Respiratory Tract Infections

Pulmonary Hypertension

Sleep-disordered breathing

GERD/Aspiration

Lower Respiratory Tract Infections

- Pneumonia a leading cause of death
- Respiratory tract infection is the most common recurrent problem giving rise to ill-health in children with Down syndrome
  - Selikowitz, J Pediatr Child Health, 1992
Lower Respiratory Tract Infections

- Most common reasons for admission to hospital are pneumonia, bronchiolitis and croup
  - 54% of 232 admissions over 6 years
- ICU admission required in 10%, of which 43% were for pneumonia
- Median length of stay in hospital is 2-3 times longer than for children without Down Syndrome
  - Hilton, J Paediatr Child Health, 1999
- OR for hospitalization 3.24 with Down Syndrome and heart disease
  - Kristensen, Arch Dis Child, 2009

Contributing factors:
- Chronic rhinitis
- Nasal and oral secretions poorly controlled
- Poor cough
- Airway obstructive lesion/compression by large heart
- Immune defects
- GERD/aspiration

Immunodeficiency

- Immune system derangements evident:
  - ↑ susceptibility to infection
  - ↑ mortality rate from infections
  - ↑ frequency of HBs Ag carriers
  - ↑ frequency of malignancies (leukemia)
  - ↑ frequency of auto antibodies (thyroid)
**Immunodeficiency**

*Cell-Mediated Immunity*

- Defective differentiation of T-cell lineage during intrathymic maturation resulting from lack of thymic hormone factors
  - Duse, Thymus, 1980
- Low # & activity of helper/inducer T-cell subsets → defective production of antibodies against certain antigens

*Humoral Immunity*

- Defective antibody responses to common antigens and influenza vaccine
- Hypogammaglobulinemia and IgG subclass deficiencies common
- Over-expression of superoxide dismutase-1 → impairment of neutrophil killing activity → susceptibility to bacterial infections
- Low serum zinc → impairment of immune response (co-factor for T-cell activation)
  - Treatment improves some immunologic parameters and may decrease infections
  - Licastro, J Intel Disability Research, 1994

**Pieces of the Puzzle**

- Structural abnormalities
- Lower Respiratory Tract Infections
- Pulmonary Hypertension
- GERD/Aspiration
- Sleep-disordered breathing
GERD/Aspiration

• Common problem encountered clinically, but little literature

Aspiration from above

• Retrospective chart review:
  – 19 patients, 16 referred for r/o aspiration
  – Underwent video fluoroscopic feeding study
  – 10 aspirated thin liquids, 8 silent aspirators.
  – None aspirated on thick liquids
    » Frazier, Developmental Med and Child Neuro, 1996

GERD/Aspiration

GERD

• 9% prevalence of GERD in adult hospital-based Down Syndrome clinic
  » Wallace, J Intell Dev Dis, 2007

• My experience: HIGHER prevalence in children referred to Respirology clinic for “recurrent pneumonia” or OSA

• 43% have serious complications from GERD
  » Moore, Pediatr Surg Int, 2008

GERD/Aspiration

GERD

• Treatment study comparing Nissen fundoplication with medical treatment with H2 blockers:
  – found fewer complications & readmissions with surgery
  – BUT had suboptimal medical management
    » Thompson, J Ped Surg, 1999

No clear answer regarding optimal treatment
Airway Obstruction

**Contributing factors**

- **Pharyngeal obstruction**
  - macroglossia, high arched palate, micrognathia, tonsillar hypertrophy
- **Functional Problems**
  - velar hypotonia, mucosal dryness, obesity
- **Nasal Obstruction**
  - narrow nasal airway, adenoid hypertrophy, rhinosinusitis
- **Malacia**
  - Pharynx, larynx, trachea
- **Subglottic stenosis/↓ airway size**

  » Clin Peds, 2004

Airway Obstruction

**Most Common Causes:**

- **Laryngomalacia** if < 1 month old

- **OSA** if > 2 years

OSA

• 40-80% have OSAS with nocturnal oxygen desaturation

• 55-97% of children with Down Syndrome have OSA
  > de Miguel-Diaz, Sleep, 2003; Shott, Arch Otolaryngol, 2006; Fitzgerald, Arch Dis Child, 2007; Ng, Arch Dis Child, 2007

• Poor correlation between parental impressions of sleep problems and sleep study result (50% error)
  > Shott, Arch Dis Child, 2006

• Over time all subjects had progression of sleep-related symptoms and persistent or worse OSA documented on PSG
  > Dyken, Arch Pediatr Otolaryngol, 2003

Other Sleep Disturbances

• Respiratory disturbance index is higher: sleep significantly fragmented with greater number of arousals

• More restless sleep: more leg kicks
  > Levanon, J Pediatr, 1999

Other Sleep Disturbances

• 66% of one series also had hypoventilation
  > Marcus, Peds, 1991

• Central sleep apnea more common than in controls and may predominate over obstructive events
  • ? Immaturity of brainstem control of respiration
    > Ferri, J Sleep Res, 1997
OSA

Clinical Features:
- Hx of snoring and difficulty breathing during sleep
- Retractions, paradoxical breathing, episodes of increased respiratory effort associated with lack of airflow (pauses in snoring)
- Gasping, choking, movement, arousal

Often under-recognized
- 68% have no clinical features

Risk factors for OSA:
- Age < 8 years (OR 3.36)
- Male (OR 3.32)
- Tonsillar hypertrophy (OR 5.24)
- ? BMI
  » Miguel-Diaz, Sleep, 2003

No association:
- Adenoid hypertrophy
- Previous T&A
- Congenital heart disease
- Malocclusion
- Macroglossia
  » Miguel-Diaz, Sleep, 2003
OSA

• **Sleep Study** = gold standard

- Oximetry can have false negatives, but detects severe OSA
  - > Brouillette, 2000

- Nap polysomnograms can underestimate severity
  - > Marcus, Peds, 1991

- Cine-MRI dynamic airway imaging can identify site of obstruction
  - > Shott, 2004

OSA

- **Treatment**

  • **T & A**
    - Fails in 30-50%
    - Glossoptosis 63%, macroglossia 74%
    - Hypopharyngeal collapse remains in 22%
    - Recurrent enlarged adenoids 63%
    - Enlarged lingual tonsils 30%
    - Often needs overnight stay in hospital post-op as co-morbidities
      - > Donnelly, 2004
OSA

Treatment

• CPAP/BiPAP
  – My experience:
    • Can be successful in the majority
    • PLAY – acclimatization to mask and pressure takes time
    • Tolerance builds over time
  – With time many develop hypoventilation

OSA

• UPPP & tongue reduction
  – results less impressive
  – < 25% success b/c of muscular hypotonia

• Lingual tonsils
  – Enlargement common if persistent OSA after T&A
    ➤ Fricka, Pediatr Radiol, 2006

• Tracheostomy

• GERD a co-morbid feature in 59-81%

OSA

Complications

• Impaired daytime functioning

• Pulmonary hypertension
Pieces of the Puzzle

- Structural abnormalities
- Pulmonary Hypertension
- Lower Respiratory Tract Infections
- GERD/Aspiration
- Sleep-disordered breathing

Pulmonary Hypertension

- Develops and progresses more rapidly to irreversible pulmonary vascular change in Down syndrome

- Contributing factors:
  - Chronic upper airway obstruction
  - Recurrent pulmonary infection
  - Alveolar hypoventilation
  - Congenital heart disease (10-100%)
  - Failure of neonatal pulmonary vascular remodeling (PPHN)

  » Shah, J Perinat Med, 2004

Pulmonary Hypertension

- 90% of children with Down syndrome and cardiac abnormalities vs. 24% of controls with similar CHD had abnormally high pulmonary arterial pressure. Children with T21 were younger on average than controls.

- 1 year after VSD repair pulmonary artery pressure remained elevated in ¾ with Down Syndrome vs. 14% of controls

  » Chi et al., J Peds, 1975
Pulmonary Hypertension

- Pulmonary artery changes were compared for children with simple cardiac anomalies with and without T21
- Pulmonary arteries of children with Down syndrome had:
  - Earlier development of intimal changes
  - More severe intimal changes
  - Less medial hypertrophy – makes PA’s more susceptible to moderate pressure loads

➤ Pulmonary artery changes predispose to earlier and more severe pulmonary vascular disease compared to controls
  > Yamaki, Am J Cardiology, 1983

Pieces of the Puzzle

Structural abnormalities

Lower Respiratory Tract Infections

Pulmonary Hypertension

GERD/Aspiration

Obstructive Sleep Apnea

Putting the Puzzle Together

Structural abnormalities

Lower Respiratory Tract Infections

Pulmonary Hypertension

GERD/Aspiration

Obstructive Sleep Apnea
Evaluation of the Child with Down Syndrome

• Respiratory Tract Infections
  – ? Recurrent vs. usual number
  – ? Single location or diffuse: review CXRs
  – Predisposing factors:
    » Immunodeficiency
    » Aspiration
    » Structural Abnormalities
    » Chronic sinusitis
    » Congenital heart disease

• GERD/Aspiration
  – From below: UGI, milk scan, pH probe
  – From above: OT feeding study

• Sleep Disordered Breathing
  – Overnight oximetry – useful screen, but if negative does not rule out OSA
  – Polysomnography is gold standard

Shh…may be silent

• Pulmonary Hypertension
  - Screen if congenital heart disease, OSA or hypoventilation
  - ECG – to look for right ventricular hypertrophy
  - Echocardiogram – to estimate right ventricular pressure
  - Cardiac Catheterization – gold standard, but more invasive
Resolution of the Case

• 6 y.o., Down syndrome, previous AVSD repair
• Cough for 3 weeks following URTI, fever, respiratory distress
• Snores at night, increasingly restless sleep, daytime fatigue, poor concentration at school
• On exam: O$_2$ sat 93% in R/A, RR 30, mild indrawing, crackles RUL
• CXR: RUL infiltrate, subpleural cysts, normal heart size

Resolution of the Case

• 6 y.o., Down syndrome, previous AVSD repair
• Cough for 3 weeks following URTI, fever, respiratory distress
• Snores at night, increasingly restless sleep, daytime fatigue, poor concentration at school
• On exam: O$_2$ sat 93% in R/A, RR 30, mild indrawing, crackles RUL
• CXR: RUL infiltrate, subpleural cysts, normal heart size

Resolution of the Case

• 6 y.o., Down syndrome, previous AVSD repair
• Cough for 3 weeks following URTI, fever, respiratory distress
• Snores at night, increasingly restless sleep, daytime fatigue, poor concentration at school
• On exam: O$_2$ sat 93% in R/A, RR 30, mild indrawing, crackles RUL
• CXR: RUL infiltrate, subpleural cysts, normal heart size
Resolution of the Case

- 6 y.o. †, Down syndrome, previous AVSD repair
- Cough for 3 weeks following URTI, fever, respiratory distress
- Snores at night, increasingly restless sleep, daytime fatigue, poor concentration at school
- On exam: O₂ sat 93% in R/A, RR 30, mild indrawing, crackles RUL
- CXR: RUL infiltrate, subpleural cysts, normal heart size

Case Resolution

- URTI → Cough, ↑ upper airway obstruction
- ↑GERD → Aspiration Pneumonia
- OSA → ↓ daytime performance
- Pulmonary Hypertension
The End

Now that all the pieces are put together...