Lung Function and Pulmonary Disease in Ataxia Telangiectasia.

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The A-T gene has been identified since 1995.

As of today, however, no treatment or cure for the primary disease is available.

Despite that – improvements in quality of life and overall survival are potentially possible by limiting secondary sequelae of the disease process.
2005-2007

- 35 deaths in US*
  - 17 respiratory related
    - Average age of death 19 years
  - 11 malignancies
  - 1 congestive heart failure
  - 6 unknowns

*A-T Clinical Center and the A-T Children’s Project
Why do individuals with A-T have pulmonary complications?
Secondary effects of A-T on the lungs

- **Neuro-degeneration**
  - Suboptimal respiratory muscle strength due to coordination problems
  - Impaired airway clearance due to weak cough
  - Abnormal swallow and aspiration

- **Immune defects**
  - Recurrent sino-pulmonary infections from immune deficiency
  - Autoimmunity and interstitial lung disease
Secondary effects of A-T on the lungs

- Sensitivity to oxidative stress
  - Constant environmental stress to the lung

- Increase in pro-inflammatory cytokines

- Abnormal injury repair
  - Fibrosis from radiation and drug toxicity
  - Bronchiectasis from recurrent infections
Pulmonary Disease and A-T

Respiratory complications may account for up to 1/3 of A-T deaths

- Sino-Pulmonary infections and Bronchiectasis
- Bulbar and respiratory muscle weakness vs. muscle incoordination
- Autoimmunity and Drug Toxicity
Bronchiectasis

- Sino-pulmonary disease is common in A-T
- Recurrent infections can lead to bronchiectasis
- Immunodeficiency contributes to an increased incidence of sino-pulmonary disease in A-T
- Treatment should include aggressive use of antibiotics and IVIG when appropriate
Interstitial Lung Disease

- Interstitial lung disease (ILD) and autoimmunity
  - 10% of individuals with common variable immune deficiency develop ILD secondary to autoimmunity
  - Incidence of ILD in people with A-T is unknown

- CT findings of ILD
  - pulmonary nodules

- In the early stages ILD may be responsive to steroids (Schroeder et al., Ped Pulm, 2005)
  - Increased risk of secondary spontaneous pneumothoraces with advanced disease
Serum KL-6 as a biomarker for interstitial lung disease?

- KL-6 is a mucin-like glycoprotein expressed on type 2 epithelial cells and bronchiolar epithelial cells
- Increased levels of serum KL-6 associated with ILD
- Higher levels of KL-6 are associated with an increased mortality from ILD
- Monitoring serum KL-6 levels in A-T may be useful diagnostically and as a biomarker for ILD disease progression

Satoh et.al., J Intern Med, 2006
Drug Toxicity and Lung Fibrosis

- Individuals with A-T have increased sensitivity to ionizing radiation and chemotherapy.
- Treatment of lymphoid malignancies in A-T individuals is associated with pulmonary decline.
  - The lung is at high risk for drug toxicity during treatment.
  - Lung fibrosis can lead to end-stage respiratory failure.
  - Protocols for the treatment of malignancies such as lymphomas should be modified to limit drug toxicity to the lung—(rituximab may be useful).
Are there other risk factors associated with rapid lung function decline in A-T?
What else may influence lung function in A-T?

- **Genetic factors**
  - Modifier genes or gene polymorphisms associated with better or worse lung function

- **Environmental factors**
  - Cigarette smoke or pollution?
  - Recurrent aspiration

- **Developmental factors**
  - Lower respiratory tract infections at an early age?
  - Earlier onset of swallowing dysfunction?
  - Poor pulmonary function at an early age?
Factors associated with lung decline in other diseases

- **Spinal cord injuries**
  - Lung function declines with age
  - Faster decline in lung function in those with the lowest quartile for mean inspiratory pressures (MIP)

- **Parkinson disease**
  - Lung function declines with progression of primary disease process

- **Cystic Fibrosis**
  - Lung function is worse in those with
    - Poor nutrition
    - Lower pulmonary function at an early age
    - In females

Stolzmann et al., AJRCCM, 2008.
Corey et al., J Peds 1997
Can we identify individuals with A-T who may be at risk for pulmonary complications or a rapid decline in pulmonary function?
Is Spirometry reproducible in individuals with A-T?

- 10 subjects with A-T performed spirometry on three consecutive occasions
  - average time interval between the first and last spirometry measurement was 6.3 months (SD, ± 2.4 months)

McGrath-Morrow et.al, Peds Pulm, 2008
Flow Volume Curves

Normal

A-T

A-T

www.ebme.co.uk/arts/spiro/Image62.jpg
Reproducibility of Spirometry

- The intra-class correlation coefficients (R) for FVC, FEV1 and FEV1/FVC ratio were 0.974, 0.963 and 0.821 respectively.

- The lower 95% confidence limit of R for FVC, FEV1 and FEV1/FVC ratio were 0.939, 0.914 and 0.631 respectively.

* (an R > 0.75 is consistent with good reproducibility)
Conclusions

- Males and Females with A-T had low %FVC and %FEV$_1$ compared to normal values.
- Females with A-T had lower %FVC and %FEV$_1$ compared to their male A-T counterparts.
- Low %FVC and %FEV$_1$ values may increase risk of pulmonary problems during respiratory illnesses or stresses.
Markers for Respiratory Muscle Strength

- Measurement of maximal inspiratory pressure (MIPs) and maximal expiratory pressure (MEPs)
  - Decline in MIPs and MEPs has been found as a marker for disease progression and respiratory failure in individuals with neuromuscular disorders
  - Low MEPs associated with poor cough and respiratory clearance
Conclusions

- MIP and MEP values are modestly decreased in adolescents with A-T
- Findings suggest some people have functional impairment of respiratory muscle strength
- Are there exercises or maneuvers that can help strengthen or maintain respiratory muscle function?
How else can we identify individuals who may be at risk for pulmonary complications?
Lung Volume Measurements

- **Body plethsmography**
  - Requires a body box - wheel chairs often do not fit
  - Breathing maneuvers may be hard to do

- **Helium Dilution**
  - Easier to perform
  - Measurement of FRC is independent of effort
  - May underestimate lung volumes in people with air trapping
  - Equipment is not available everywhere.
Helium Dilution

Beginning of test

Several minutes into test

oac.med.jhmi.edu/.../GasDilutionInhaleExhale.GIF
Conclusions

- % VC is decreased in A-T adolescents
- Females have lower % VCs then males with A-T
- % RV is increased in adolescents with A-T suggesting an inability to expire completely to RV
- % TLC and % FRC are close to normal
- Individuals with low %TLCs may be at increased risk for pulmonary complications

McGrath-Morrow et.al. Ped Pulm. 2008
Are overnight sleep studies useful in adolescents with A-T?
Results of overnight polysomnography

- Decreased sleep efficiency
- Sleep-related upper airway obstructions were not common
- Mild sleep-related hypercapnia was found in some
  - May represent early sleep-related hypoventilation
- Overnight polysomnography should be considered in adolescents with A-T, particularly in those in which there is a clinical suspicion of sleep-related breathing abnormalities or progressive lung disease

McGrath-Morrow et.al., Ped Pulm. (in press)
IL-8 levels in children with A-T
Increased IL-8 levels in serum of A-T adolescents

Are high circulating levels of the pro-inflammatory cytokine IL-8 associated with disease activity?
Macrolides, cytokines and inflammation

- Activation of NF-kappa β - increases the proinflammatory cytokines, IL-6 and IL-8
- Azithromycin has been shown to decrease activation of NF-Kappa β pathway and inflammatory cytokines (Aghai et.al., Ped Res, 2007, Tamaoki et. al, Am J Med, 2004)
- Azithromycin has immunomodulatory effects that may benefit inflamed airways (Majima, Am J Med, 2004)
Fluticasone

- In vitro, fluticasone inhibited LPS-induced IL-6 and IL-8 in CF bronchial cells (Escotte et. al., Eur Respir J, 2003)
- Fluticasone decreases inflammation through reduction of IkB-α/β
Future Directions

Can we improve airway clearance and strengthen expiratory muscle strength in children and adolescents with A-T?
Bulbar Dysfunction is common in A-T

- Peak cough flows may be decreased in individuals with bulbar dysfunction
- Bulbar dysfunction is associated with swallowing abnormalities and aspiration
- Reduced expiratory flows due to bulbar dysfunction and decreased respiratory muscle strength may impair the ability to clear airway secretions
  - particularly during respiratory tract infections

Winck et al., Chest, 2004
Airway clearance devices

- Acapella
  - Requires a good mouth-seal
  - Provides positive expiratory pressure
  - Exhaling through the device creates pressure oscillations in the airway which mobilizes airway secretions

- Therapy vest
  - Air pulsates through the vest to mobilize airway secretions from the lower airways to larger airways to be coughed up
Airway clearance devices

- **Cough-assist device**
  - Delivers alternating positive then negative pressures to the airway to mobilize airway secretions

- **EMST device**
  - Provides consistent pressure load during expiration, unlike the acapella
  - May stabilize or increase expiratory muscle strength
  - May improve cough flows, breathing, swallow and speech
Are we aggressively treating sino-pulmonary infections in A-T?
Sino-pulmonary infections in A-T

- Sino-pulmonary infections may be clinically silent in A-T
  - Chronic congestion may be associated with sino-pulmonary disease
  - More aggressive treatment of sino-pulmonary may decrease pulmonary sequela
- Low-dose radiologic imaging may be useful in diagnosing sino-pulmonary disease
- Sinus MRI may be considered
Recommendations for respiratory care in children and adolescents with A-T

- Spirometry on an annual basis (>12 years of age)
  - consider lung volume studies in those with low FVCs
- Aggressive treatment of sino-pulmonary disease
- Appropriate vaccinations
- Consider pulmonary referral before major surgery
- Consider sleep study in patients with:
  - daytime hypoxia, suspected sleep related hypoxia and/or hypoventilation
Recommendations for respiratory care in children and adolescents with A-T

- Consider pulmonary clearance techniques when appropriate
- Awareness of aspiration as a trigger for chronic lung disease
- Screen for interstitial lung disease in patients with chronic respiratory symptoms and decreased vital capacities
Clinical Classifications of Lung Disease in A-T
Chronic Sino-Pulmonary Disease

- Frequent sino-respiratory infections
- Moist cough
- Chronic or Intermittent chest congestion
- Immunodeficiency
- Bronchiectasis

Treatment options

- IV or Oral antibiotics
- Chest clearance techniques (therapy vest, acapella, Nebs)
- Intravenous Immunoglobulins if indicated
- Consider chronic prophylactic antibiotics, i.e.-azithromycin
- Aggressively treat chronic sinus infections often requiring 4-6 weeks of antibiotics
Neuromuscular and Bulbar Weakness

-Trouble clearing secretions with colds
-Weak cough
-Intermittent dry cough
-Congestion or cough with meals
-Poor weight gain
-Weak swallow

Treatment options

-Avoid aspiration with feeds
-Monitor weight and increase calories
-Consider gastric tube feeds
-Monitor for gas exchange abnormalities particularly with colds or during or after operative procedures- may consider Bipap
-Use of acapella

Early treatment of respiratory infections
Interstitial Lung Disease

- Dry cough
- Fast breathing
- Poor response to an adequate course of antibiotics
- Fatigue with activity
- Chest CT consistent with an interstitial lung disease process

↓ Treatment options

- Consider extended trial of oral steroids if radiological and clinical symptoms suggest interstitial lung disease
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