The Link Between Viruses and Asthma

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Objectives:

At the end of this session, the participant would be able to:

• Explain that respiratory viruses influence the immune system

• Discuss the mechanisms by which the viral infections affect the airway

• Explain the potential for developing new specific treatments for virus-induced asthma
Introduction

• Management in the young
  • extrapolated from what is known in asthma in older children

• Past decade
  • there has been an exponential rise on asthma research in young children

• number of National Institutes of Health (NIH) funding have focused on asthma research in the young
**Pathophysiology**

- airway hyperactivity and bronchoconstriction
  - reversible with bronchodilators and inhaled corticosteroids
- persistent changes in airway structure
  - sub-basement fibrosis, epithelial cell injury, smooth muscle atrophy, angiogenesis, mucus hypersecretion (remodeling)
Hygiene hypothesis

Factors favoring the Th1 phenotype:
- Presence of older siblings
- Early exposure to day care
- Tuberculosis, measles, or hepatitis A infection
- Rural environment

Factors favoring the Th2 phenotype:
- Widespread use of antibiotics
- Western lifestyle
- Urban environment
- Diet
- Sensitization to house-dust mites and cockroaches

Th1

Protective immunity

Cytokine balance

Th2

Allergic diseases including asthma
Asthma in the young?
Reactive Airway Disease

- liberally used in the pediatric world
  - when young children presents with wheezing and coughing episodes
- non-specific terms:
  - recurrent pneumonia
  - wheezy bronchitis
  - viral bronchiolitis
Reactive Airway Disease

• fails to follow through with the diagnosis of possibly having asthma

• a false security in physicians
  • result in either over or under treating patients
Editorial

“Reactive Airways Disease”

• A Lazy Term of Uncertain Meaning That Should Be Abandoned

• difficulty with establishing a diagnosis of asthma in some situations?

• versus airway hyperreactivity (bronchoconstrictor response)
  • methacholine, exercise, cold air

Wheezing phenotypes

BHR = bronchial hyperresponsiveness

Tucson Children’s Respiratory Study: wheezing phenotypes and natural history

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Description</th>
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<tbody>
<tr>
<td>Never wheezed (51.5%)</td>
<td>Not associated with asthma</td>
</tr>
<tr>
<td>Transient early wheezers (19.9%)</td>
<td>Only wheezed &lt;3 yo</td>
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<td></td>
<td>Not associated with asthma (by 22 yo), but theoretical increased risk of COPD</td>
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<tr>
<td>Persistent wheezers (13.7%)</td>
<td>Wheezed at &lt;3 yo and 6 yo</td>
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<tr>
<td></td>
<td>40% non-atopic</td>
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<td></td>
<td>“Non-atopic wheezers”</td>
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<td>RSV at &lt;3 yo associated with wheezing up to 11 yo (no significant risk at 13 yo)</td>
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<tr>
<td>Late-onset wheezers (15%)</td>
<td>Wheezed at 6 yo</td>
</tr>
<tr>
<td></td>
<td>Atopic</td>
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<tr>
<td></td>
<td>High risk for asthma</td>
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<tr>
<td></td>
<td>• 70% with asthma at 22 yo were persistent or late-onset wheezers</td>
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<td></td>
<td>• 49% of subjects with h/o asthma dx or current wheeze by 22 yo</td>
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<tr>
<td></td>
<td>• 31% with active asthma at 22 yo</td>
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Asthma predictive index

• developed over 10 years ago
  • based on Tucson Children’s respiratory birth cohort of 1247 children
  • to date, one of the major asthma predictive indices used in multiple longitudinal studies
• easy accessibility and convenience in a primary care settings

J Allergy Clin Immunol 2010;126:212-6
Asthma predictive index (API)

• Major criterion:
  • History of physician diagnosed asthma reported by parents
  • Physician diagnosed of eczema

• Minor criterion:
  • Physician diagnosed allergic rhinitis
  • Wheezing apart from colds
  • Eosinophilia(≥4%)
Asthma predictive index-continued

• A lose index
  • <3 episodes of wheezing/ year
  • one major or 2 minor criteria

• A stringent index
  • having >3 episodes of wheezing/ year
  • one major or 2 minor criteria

*a positive stringent index with 77% chance of developing asthma at age 6 years*
modified Asthma Predictive Index (mAPI)

- created based on 285 subjects
- incorporated
  - allergic sensitization to >1 aeroallergen as part of the major criterion
  - allergic sensitization to milk, eggs or peanuts as a minor criterion which replaced physician diagnosed allergic rhinitis

*J Allergy Clin Immunol 2004;114:1282-7*
The Allergic March

Typical evolution of allergic diseases

Adapted from Holgate S. Church MK, eds. Allergy. London: Gower Medical Publishing, 1993

Allergy 55 (7), 591-599 (2000)
Maternal smoking

• may increase airway reactivity
• non-reversible changes in the anatomy of the airway
  • algorithm based on longitudinal studies done in Finland and Sweden
• maternal smoking was added as part of the major criteria
  • importance of early sensitization to environmental allergen and subsequent development of asthma

Development and Variability of Asthma

Genetic ancestry
Gene-gene interactions

Genes

Environmental factors
Demographic factors
Social factors

Gene-environment interactions

Asthma
Evidence from birth cohort studies

• PROTECTIVE
  • Siblings (birth order)
  • Dust
  • Microbes
  • Pets
  • Dust from farm animals

• INCREASED RISK
  • Urban residence
  • Smaller family size
  • Cesarean section births
  • Use of antibiotics during pregnancy
Hygiene hypothesis

• 1989: why asthma and allergic disorders were increasing in industrialized countries?

• Early-life exposures to viral and bacterial organisms and products (endotoxins) - ‘shape’ and train the immune system

- elimination of these exposures results in a shift towards an inflammatory immune response (asthma and allergic diseases)

Charles Darwin “Evolution”

• the immune response in ‘alert/vigilant’ immune systems
  • survival advantage in a world abundant with microbes and viruses
  • attacks itself in the absence of these foreign invaders
→ resulting in increases in autoimmune diseases such as asthma
  • increase in autoimmune diseases (1950–2000), with corresponding decrease in infectious diseases
Divergent outcome of TH2 responses

Industrialized countries (low pathogen exposure)

- Vaccines, hygiene and antibiotics: little TH1 stimulation, increase in TH2.

- Low exposure to pathogens: weak regulatory network

- Allergic responses: Asthma, Rhin conjunctivitis

- Mucus production

- Smooth muscle cell contraction

Developing countries (high pathogen exposure)

- Helminth infections: strong stimulation of TH2 responses.

- High exposure to pathogens: strong regulatory network

- Seropositive for allergens: but little allergic disease

Epigenetic changes

Environmental exposures

DNA methylation

histone acetylation

micro-RNA changes

altered immune response to microbes

GWAS

• genome-wide association studies (GWAS)
• numerous genes associated with asthma and related phenotypes
  • GSDMB/ORMDL3 region (17q12-q21 region)
  • NFKBI, IL1R2, LBP, IL18RAP and TLR1
• Interact with viral infections in the first year of life
  • modify the risk for asthma and allergic diseases

Th1 and Th2 responses

Non-atopy

Atopy

Infectious

Allergic

Non-atopy

Atopy

Infectious

Allergic
Th1 and Th2 responses start in utero

- infant cord blood: predominant Th2 profile
- lack of exposure to bacteria in early infancy
  - locks the immune system into the predominantly Th2 state (seen in atopic individuals)
  - viral infections that are associated with wheezing increase the risk for developing asthma

Viral Infections
Variety of respiratory viruses

- Influenza
- Parainfluenza
- Respiratory Syncytical Virus
- Human Metapneumovirus
- Rhinovirus
- Adenovirus
- Enterovirus
Viral infections

• well recognized risk factor for asthma
• may cause up to 60% of asthma exacerbations
• Questions are:
  • viruses are causal, impacting and modifying the growth and development of the immune system?
  • viral infection agitates and initiates symptoms in a genetically susceptible individual with impaired lung function
Tucson Children’s Respiratory study (1980s)

• 1246 children from birth to date
• 32% who develops a lower respiratory illness (LRI) will **wheeze** especially when it occurs in the first year of life
• etiologic agent (through viral cultures and direct immunofluorescence antigen detection)
  • RSV and parainfluenza virus type 3
Tucson birth cohort study

- incorporated into minor criterion
  - wheezing induced by viruses
- <3 years of age with RSV infection
  - presented with bronchiolitis or pneumonia were 3-5 times more likely to develop wheezing at 6 years of age but no rise in risk by teenage years

Other respiratory viruses

• metapneumovirus bronchiolitis
  • had similar clinical presentation as well as outcome as RSV bronchiolitis
    • similar effect on the airway in terms of airways sensitization and hyperactivity
    • viruses may possibly alter normal lung development
    • or act as a trigger on those genetically predisposed infants with pre-existing aberrant airway function or immune system

“Two-hit” hypothesis

• viral infections promote asthma
  • mainly in children **already predisposed** to getting asthma
  • more severe viral infections
  • allergic sensitization precedes wheezing

• Recent study:
  • serum of 287 asthmatic children
  • increased levels of serum titers for allergen-specific IgE
    → increasing the probability of wheezing with human rhinovirus (HRV) infection

Viruses associated with asthma susceptibility

• Numerous viruses
• Most frequently associated
  • RSV (respiratory syncytial virus)
  • HRV (human rhinovirus) – common cold
Respiratory syncytial virus (RSV)
Early studies and recent research

• Earlier: focused on RSV as the primary candidate for asthma susceptibility and exacerbation

• Recently: wheezing episodes in response to HRV infection have a stronger association than RSV with future wheezing and asthma in early life

Viruses interact with host susceptibility factors to promote recurrent wheeze and asthma development. The nature of these interactions are both virus and age specific. Interactions between lung and immune factors play a role in determining the severity of viral infections and long-term outcomes.

AHR: airway hyperresponsiveness; LRI: lower respiratory tract infection.
Genes interacting with viral infections

• Recently published studies (birth cohorts):
  • Canadian Asthma Primary Prevention Study (CAPPS)
    • TLR2 and ILIR2 x picornavirus = atopic asthma
    • LBP x picornavirus = airway hyper-responsiveness (AHR)
    • IL18RAP and TLR x parainfluenza = AHR
    • NFKBIB x RSV = AHR

• picornavirus - enterovirus and rhinovirus;
• respiratory syncytial virus (RSV)
Genes interacting with viral infections -continued

- Childhood Origin of Asthma (COAST)
- Copenhagen Prospective Study on Asthma in Childhood (COPSAC)
  - 17q21 variations x HRV = wheezing illness in early life
- human rhinovirus (HRV)
The common cold in the emergency department (ED)

- children with acute wheezing and viral infection in the ED
  - Human rhinovirus (HRV) was the most common virus (68.5%)
  - HRV-C was the most common HRV species
    - higher risk for subsequent hospital admissions and a higher proportion of prior emergency room visits (compared to HRV-A and HRV-B)
    - greatest risk for subsequent hospitalization: **atopic children** infected with HRV-C

Why is there mild bronchiolitis and severe bronchiolitis?

- Inherited variation in innate immune response genes → interact with viral infection → predispose to disease

- NFKBIA - central hub in transcriptional responses of childhood lung disease

  - RSV infection, asthma and bronchopulmonary dysplasia
  - Genetic variation in the promoter of NFKBIA is associated with differential susceptibility to severe bronchiolitis, AHR, and severe bronchopulmonary dysplasia

Airway remodelling

• pulmonary $^3$He MRI
• regional patterns of airway obstruction at age 9 and 10 years (COAST study) in children with asthma

→ Associated with child’s lung function and prior history of viral illness
(Viral infection, immune system response and airway remodeling)

J Allergy Clin Immunol 2013; 131:369–376 (e1-5).
Promising target and potential biomarker

- DNA methylation (form of epigenetic regulation)
  - host cell defense mechanism, helping to keep integrated viral sequences in a repressed state
  - regulation of cell-specific gene expression in the immune system

What can we do?

• Prevention strategies
  • breast-feeding in infancy
  • introduction of solid food after the fourth month of life
  • the avoidance of smoking and passive smoke exposure of children
Summary

• Asthma is complex with many interacting components
  • local and systemic immune responses
  • genetic variants and epigenetic phenomenon
  • environmental exposures
    • viral infections in early life
    • changes in our environment over the past decades
  • potential interactions of these factors
• knowledge of host-virus interactions are important to design potential treatments to alter immune response
JS is a 9 month old boy with Down’s syndrome

• recent infections of RSV
• admitted for management of respiratory distress due to bronchiolitis from rhino/enterovirus and metapneumovirus
• superimposed bacterial pneumonia
Findings concerning for multifocal pneumonia in the right lung and possible atelectasis at the left upper lung zone.
Questions

• Was chest x-ray indicated?
• Will you treat the pneumonia with antibiotics?
• Continuous versus spot oximetry checks overnights?
• Supplemental oxygen required?
• Possible need for oxygen supplementation for travel?
• When do you anticipate to discharge home to Florida?
CB is a 10 month old baby boy

- admitted to the floor and placed on bronchiolitis protocol
- alerted by the respiratory therapist, no improvement on Albuterol every 2 hours
- multiple congenital anomalies
- remains in respiratory distress despite the current interventions
- Requiring supplemental oxygen
Recommendations

1. Alternate Albuterol 2.5mg and Atrovent 0.5mg q2 hours.
2. Continue prednisolone for 3 more days then start taper.
3. Start budesonide 0.5mg BID
4. Start neosynephrine to decreased nasal congestion.
5. Please make omeprazole 5mg BID
6. Continue aggressive chest physiotherapy.
7. Repeat CXR if respiratory status worsens or does
Interval worsening of bilateral perihilar predominant and retrocardiac airspace opacity suspicious for multifocal pneumonia.
Primary immunodeficiency secondary to genetic mutation

• APDS2 is a newly defined combined immunodeficiency a gain-of-function mutation of the PI3K enzyme, that is involved in lymphocyte development and activation

• patients have recurrent severe respiratory infection early in life that may cause bronchiectasis.
Hospital course

• back to back admission, with respiratory viral infections, in addition, because of his congenital abnormalities, he has poor airway clearance
• On follow-up, intermittent increased work of breathing and O2 requirement, which seems to resolve with increased bronchodilators and airway clearance
• Repeat CXR today - still with significant perhilar densities, right more than left
• Aggressive airway clearance, chest PT
• Ensure that he gets frequent repositioning
• Continue with alternate Atrovent and Albuterol as bronchodilators

Per Peds Infectious and Immunology recommendation, consider to...
KG is a 4 month old former 24 week premie

- Recently discharged from NICU
- bronchopulmonary dysplasia, chronic supplemental oxygen use, ROP, GERD, grade II/IV IVH
- admitted with increase oxygen requirement and apnea in the setting of coronavirus bronchiolitis and dehydration
- Upon discharge from the pediatric floor, apneic bradycardic episode requiring chest compressions
Differential diagnoses

• progression of coronavirus bronchiolitis
• co-infection with another virus
• bacterial pneumonia (lower on list in absence of fevers and rapidly weaning on O2 support)
• mucous plugging
• obstructive positioning while in carseat, floppy airway,
• arrhythmia (?heart block)
• associated with underlying neurologic disease
• related central apnea related to the acute viral illness. This has been reported in RSV and rhinovirus.
Recommendations

• Wean O2 as tolerated
• Requested at home mother monitor sleeping RR, HR and O2 saturation to get baseline when well.
• Continue Hydrochlorothiazide. Continue to monitor HCO3 and pCO2. Would consider starting Spironolactone or KCl.
• Continue Pulmicort and albuterol as needed
• Continue PPI and H2 blocker. Would consider starting second line agent like Bethanechol
Thymic silhouette is unchanged from prior. Interval worsening of patchy opacities bilaterally concerning for multifocal pneumonia superimposed on BPD.
SU is a 2 year old admitted for acute viral respiratory illness

- rhino/enterovirus positive
- With history of prior respiratory/wheezing episode, prescribed Albuterol nebulizer in the past by PMD.
- Patient has a significant history of being an ex 27 weeker, with prolonged NICU stay.
Right base/infrahilar focal opacity may represent a small focal area of consolidation. Linear opacities are identified in both upper lobes and right lower lobe may represent scarring/atelectasis as a sequel of prolonged ventilation/bronchopulmonary dysplasia, correlate clinically.
Recommendations:

• Given his history of ex-27 weeker premature birth with significant NICU history, and patient already presented with prior respiratory event needing Albuterol thru PMD.

• Although there is no significant history of asthma, we would follow patient's respiratory trend closely. Currently, would not recommend controller medication, but would strongly consider this winter season should patient continue to have increased or recurrent respiratory symptoms.

• Currently, agree with current management of patient's acute RAD exacerbation.

• Follow up with Peds Pulmonary in 2 to 4 weeks. We will work with mother and follow patient closer to her home. Will be coordinating first asthma education visit with MD/NP, then subsequent follow up...
AT is a 5 month old baby girl

• pulmonary evaluation for noisy breathing
• some concerns with increased work of breathing
• no cough until 4 days ago with URI - given Azithromycin

• congestion versus wheezing
• -given Albuterol nebulizer treatments 1 month ago
• -does not seem to help
Assessment and Plan

• Overfeeding; GERD
• R/O Laryngomalacia

• Advised on spacing the formula intake 4 oz every 3 to 4 hours, instead of every 2 hours
• Head of bead elevated; GERD precautions
• Schedule UGIS/barium esophagram to rule out anatomical abnormalities
• Schedule bronchoscopy for evaluation of airway
Later, presented to ED with 3-4 days of worsening cough and congestion

- increased work of breathing that was not improving with albuterol at home. No fever. Decreased po intake.
- In ED, pt was given 3x combinebs and loading dose of steroids which was thought to improve her sx. Received additional albuterol at 2h.
- RVP + for RSV & Adenovirus
- had a normal barium swallow as part of her laryngomalacia work-up
- still awaiting bronchoscopy which will have to be done once she has improved from her acute infection
- Physical exam consisted with referred upper airway noises, no wheezing appreciated
- agreed to observe off albuterol as unclear if truly helping her symptoms
- No hypoxemia, breathing improved on admission to the floor
Bronchoscopy

Diagnostic Findings:
Mild laryngomalacia, Chronic pharyngeal inflammation
- chronic pharyngeal inflammation may be indirect evidence of irritation from reflux.

- Addressed to space feedings to every 3 to 4 hours, as they gradually increase baby pureed foods
- Zantac 1.5 ml po BID
- Upright during feeds