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

Th2

Cytokine balance

Allergic diseases including asthma

Stony Brook Children's
Asthma in the young?
Reactive Airway Disease

• Liberally used in the pediatric world
  • When young children present 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

**Asthma Predictive Index**

- Reduced Lung Function at Birth
- BHR at Birth
- Atopic Asthmatics With BHR
- IgE-Associated Wheezing/Asthma

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

<table>
<thead>
<tr>
<th>Wheezing Phenotype</th>
<th>Prevalence</th>
<th>Age of Wheezing</th>
<th>Atopic %</th>
<th>Risk of COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never wheezed (51.5%)</td>
<td>3</td>
<td>Not associated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient early wheezers (19.9%)</td>
<td>6</td>
<td>Only wheezed &lt;3 yo</td>
<td>Not associated</td>
<td>by 22 yo, but theoretical increased risk of COPD</td>
</tr>
<tr>
<td>Persistent wheezers (13.7%)</td>
<td>6</td>
<td>Wheezed at &lt;3 yo and 6 yo</td>
<td>40% non-atopic</td>
<td></td>
</tr>
<tr>
<td>“Non-atopic wheezers”</td>
<td></td>
<td></td>
<td>60% atopic</td>
<td></td>
</tr>
<tr>
<td>Late-onset wheezers (15%)</td>
<td>6</td>
<td>Wheezed at 6 yo</td>
<td>Atopic</td>
<td>RSV at &lt;3 yo associated with wheezing up to 11 yo (no significant risk at 13 yo)</td>
</tr>
</tbody>
</table>

High risk for asthma
- 70% with asthma at 22 yo were persistent or late-onset wheezers
- 49% of subjects with h/o asthma dx or current wheeze by 22 yo
- 31% with active asthma at 22 yo

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
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

Urban residence
Dust
Dust from farm animals
Cesarean section births
Smaller family size
Pets
Use of antibiotics during pregnancy
Microbes
Siblings (birth order)
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 T\textsubscript{H}1 stimulation, increase in T\textsubscript{H}2.

Low exposure to pathogens: weak regulatory network

Allergic responses: Asthma, Rhinoconjunctivitis

Mucus production

Smooth muscle cell contraction

Developing countries (high pathogen exposure)

Helminth infections: strong stimulation of T\textsubscript{H}2 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
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

\[ \rightarrow \text{increasing the probability of wheezing with human rhinovirus (HRV) infection} \]

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 and host factors

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 IL1R2 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