Natural History of Allergic Diseases and Asthma

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Outline

- Introduction
- Asthma
- AD
- AR
- Food Allergy
- Anaphylaxis
- Co-morbidities

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Introduction

• Fundamental for predicting disease onset and prognosis.
• Studies reveal a developmental ‘allergic march’ in childhood,
• from the early onset of atopic dermatitis (AD) and food allergies in infancy, to asthma, allergic rhinitis (AR), and inhalant allergen sensitization in later childhood.
Introduction

• Three prospective, longitudinal, birth cohort studies exemplify optimized natural history studies that are rich resources for our current understanding of the development and outcome of allergy and asthma in childhood:
  → Tucson Children’s Respiratory Study (CRS) in Tucson, Arizona (begun in 1980)
  → Kaiser-based study in San Diego, California (begun in 1981) and
  → German Multicentre Allergy Study (MAS) (begun in 1990).
Allergic March(1)

- The highest incidence of AD and food allergies is in the first 2 years of life.
- This is paralleled by a high prevalence of food allergen sensitization in the first 2 years of life.
- Early food allergen sensitization is an important risk factor for food allergies, AD, and asthma.
• Allergic airways diseases generally begin slightly later in childhood.
• AR commonly begins in childhood, although there is also good evidence that AR often develops in early adulthood.
• The development of AR and persistent asthma is paralleled by a rise in inhalant allergen sensitization.
Figure 2-1 Allergic march of early childhood. Period prevalence of atopic dermatitis, food allergy, allergic rhinitis, and asthma from birth to 7 years in prophylactic-treated (allergenic food avoidance) and untreated (control) groups (Kaiser Permanente; San Diego). * P ≤ 0.05; **P < 0.01. (Data from Zeiger RS, Heller S J. Allergy Clin Immunol 1995;95:1179–1190; and Zeiger RS, Heller S, Mellon MH, et al. J Allergy Clin Immunol 1989;84:72–89.)
Total serum IgE

- At birth, cord blood IgE levels are almost undetectable,
- Levels increase during the first 6 years of life. Elevated serum IgE levels in infancy have been associated with persistent asthma
- High serum IgE levels in later childhood (i.e. after 11 years of age) have also been well correlated with BHR and asthma

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Specific IgE allergen development

• Production of IgE starts in the 11th week of gestation; no specific sensitization to food or inhalant allergens can be detected in cord blood.

• The first IgE responses directed to food proteins may be observed during the first months of life and are usu to hen’s eggs and cow’s milk (maternal exposure).
Specific IgE (2)

• Strong infantile maternal responses to food proteins are markers for atopic reactivity in general and are predictors of subsequent sensitization to aeroallergens.

• Indoor inhalant allergen sensitization (i.e. cat dander, dust mites) emerges between 2 to 5 years of age,

• Outdoor inhalant allergen sensitization becomes apparent slightly later in life (ages 3 to 5yrs)
Asthma

• About 80% of asthmatic patients report disease onset before 6 yrs of age.

• Of all young children who experience recurrent wheezing, only a minority will go on to have persistent asthma in later life.
Figure 2-2  Hypothetical yearly prevalence for recurrent wheezing phenotypes in childhood (Tucson Children’s Respiratory Study, Tucson, Arizona). This classification does not imply that the groups are exclusive. Dashed lines suggest that wheezing can be represented by different curve shapes resulting from many different factors, including overlap of groups. (Modified from Stein RT, Holberg CJ, Morgan WJ, et al. Thorax 1997;52:946–952.)
<table>
<thead>
<tr>
<th>Wheezing phenotype</th>
<th>Period of wheeze</th>
<th>N(%)</th>
<th>Recurrent wheeze/cough @16y(%)</th>
<th>LFTs 1y</th>
<th>LFTs 6y</th>
<th>LFTs 16y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient early</td>
<td>&lt;3yrs</td>
<td>20</td>
<td>20</td>
<td>Lowest airflow</td>
<td>improved</td>
<td>Lower than normal</td>
</tr>
<tr>
<td>persistent</td>
<td>6rs</td>
<td>14</td>
<td>50</td>
<td>Normal</td>
<td>declined</td>
<td>Persist decline</td>
</tr>
<tr>
<td>Late onset</td>
<td>&gt;3yrs</td>
<td>15</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BOX 2-1 Key concepts

**Childhood Wheezing and Asthma Phenotypes**

- Transient early wheezing or wheezy bronchitis: most common in infancy and preschool years
- Persistent allergy-associated asthma: most common phenotype in school-age children, adults, and elderly
- Nonallergic wheezing: associated with bronchial hyper-responsiveness at birth; continues into childhood
- Asthma associated with obesity, female gender, and early-onset puberty: emerges between 6 and 11 years of age
- Asthma mediated by occupational-type exposures: a probable type of childhood asthma in children living in particular locales, although not yet demonstrated
- Triad asthma: asthma associated with chronic sinusitis, nasal polyposis, and/or hypersensitivity to nonsteroidal antiinflammatory medications (e.g. aspirin, ibuprofen); rarely begins in childhood
### Risk Factors for Persistent Asthma

**Allergy**
- Atopic dermatitis
- Allergic rhinitis
- Elevated total serum IgE levels (first year of life)
- Peripheral blood eosinophilia >4% (2 to 3 years of age)
- Inhalant and food allergen sensitization

**Gender**
- Males
  - Transient wheezing
  - Persistent allergy-associated asthma
- Females
  - Asthma associated with obesity and early-onset puberty
  - ‘Triad’ asthma (adulthood)

**Parental Asthma**

**Lower Respiratory Tract Infections**
- Rhinovirus, respiratory syncytial virus
- Severe bronchiolitis (i.e. requiring hospitalization)
- Pneumonia

**Environmental Tobacco Smoke Exposure (Including Prenatal)**
At least 4 wheezing episodes, plus:

<table>
<thead>
<tr>
<th>1 Major criterion</th>
<th>or 2 Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental asthma</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Eczema</td>
<td>Wheezing apart from colds</td>
</tr>
<tr>
<td>Inhalant allergen sensitization</td>
<td>Eosinophils ≥ 4%</td>
</tr>
<tr>
<td></td>
<td>Food allergen sensitization</td>
</tr>
</tbody>
</table>

Figure 2-3  Natural history of lung function from childhood to adulthood (Melbourne Longitudinal Study of Asthma, Melbourne, Australia). Subjects were classified according to their diagnosis at time of enrollment: no-wheeze control; mild wheezy bronchitis; wheezy bronchitis; asthma; and severe asthma. Lung function is represented as FEV₁ corrected for lung volume (FEV₁/FVC ratio). Mean values and standard error bars are shown. (Adapted from Oswald H, Phelan PD, Lanigan A, et al. Pediatr Pulmonol 1997;23:14–20; with data for ages 42 years from Horak E, Lanigan A, Roberts M, et al. BMJ 2003; 326(7386):422–423).
Atopic dermatitis (AD)

•Usu is the first clinical manifestation of the Ig E response .begins during the preschool years and persists throughout childhood
•The greatest remission in AD, 8-11 yrs; to a lesser extent 12-16yrs
•Parental h/o AD an important risk factor.
•Exclusive breastfeeding infants with a family h/o atopy for at least 3 months, protective (OR 0.58)
<table>
<thead>
<tr>
<th>AD severity</th>
<th>Initial examination</th>
<th>4 years later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhalant ± food</td>
<td>Food only</td>
</tr>
<tr>
<td>Mild</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Moderate</td>
<td>18%</td>
<td>26%</td>
</tr>
<tr>
<td>Severe</td>
<td>20%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Figure 2-5 Atopic dermatitis (AD) in young children (2 months to 3 years of age) and allergen sensitization (to food and inhalant allergens), asthma, and allergic rhinoconjunctivitis (AR) 4 years later. At enrollment, AD severity was determined, and no subjects had AR or asthma. Four years later, 88% of subjects had a marked improvement or complete resolution of AD. However, all children with severe AD at enrollment were sensitized to inhalant allergens, and 75% had asthma and/or AR. (From Patrizi A, Guerrini V, Ricci G, et al. Pediatr Dermatol 2000; 17:261–265.)
Allergic rhinitis (AR)

- Many people develop AR during childhood. Prospective birth cohort study reported a steady rise in total AR prevalence reaching 35-40% by 7 yrs.

- AR also commonly begins in adulthood. 23 yr cohort study of Brown Univ. beginning in their freshman yr, perennial AR developed in 4.8% at 7 yrs and 14% at 23 yrs of following.
AR

• Allergen skin test sensitization and asthma were prognostic risk factors for the devt of AR.
• Onset of disease in early childhood was associated with greater improvement in symptoms.
Food Allergy

• Prevalence is greatest in the first few years of life, affecting 5% to 15% of children in their first year of life.

• Most children seem to ‘outgrow’ their food allergies to milk, soy, and egg within a few years.

• Long-term follow-up studies of peanut-allergic children found that loss of clinical hypersensitivity was uncommon, especially in children with anaphylactic symptoms in addition to urticaria and/or AD.
Food Allergy

- Allergies to other nuts, fish, and shellfish are also believed to be more persistent.

- Allergen hypersensitivity to milk at 1 year of age was a risk factor for additional food allergies in later childhood.

- Food hypersensitivity in early life (i.e. to milk, egg, peanut) was found to be a risk factor for AD and, later, asthma.
Anaphylaxis

• H/o AR/asthma a risk factor for anaphylaxis to foods and latex

• Insect sting anaphylaxis is often self-limited in children, with spontaneous remission usually occurring within 4 years.
Anaphylaxis

• Those at greatest risk of persistent hypersensitivity include those with previous severe anaphylactic episodes.

• Children with mild systemic reactions to bee stings are less likely to have an allergic reaction on re-sting.

• Future anaphylactic episodes from bee stings are not likely to be severe.
Co-morbidity: Food allergy and AD

- Early Prevention of Asthma in Atopic Children (EPAAC): assessed 2200 infants with eczema for sensitization to common food and aeroallergens
  - Any food: 48.6%
  - Egg white: 41.9% (SA 47.1)
  - Cow’s milk: 27.4% (SA 28.4%)
  - Peanut: 24.4% (SA 26.8%)

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### Studies on challenge-proven food allergies in atopic dermatitis

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>location</th>
<th>No. of patients (mean age)</th>
<th>+ve SPT or IgE</th>
<th>+ve food challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burks et al (1988)</td>
<td>USA</td>
<td>165 (48 mnths)</td>
<td>60%+ve SPT</td>
<td>38.7%</td>
</tr>
<tr>
<td>Eigenmen et al (1988)</td>
<td>USA</td>
<td>63 (2.8yrs)</td>
<td>65% +ve IgE</td>
<td>37%</td>
</tr>
<tr>
<td>Eigenmen et al (2000)</td>
<td>Switzerland</td>
<td>74(2.5yrs)</td>
<td>59%+ve IgE</td>
<td>33.8%</td>
</tr>
<tr>
<td>Garcia (2007)</td>
<td>Spain</td>
<td>44(7.5 mnths)</td>
<td>61%+ve SPT/IgE</td>
<td>27%</td>
</tr>
</tbody>
</table>
Co-morbidity: AR and Asthma

- AR frequently precedes asthma, conferring a 3-7 fold increased risk for incident asthma
- Rhinitis is highly prevalent among asthmatics ranging from 55-79%, and severity of rhinitis is positively associated with asthma severity.
- Treatments for allergic rhinitis result in improvement of asthma.
- Randomized trials of immunotherapy for AR have demonstrated a reduction in asthma incidence sustained at 10 years follow-up.
- Immunotherapy for concurrent asthma/AR has resulted in marked reduction in asthma as well as AR exacerbations.

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Conclusion

• The term ‘atopic march’ refers to the natural history of atopic manifestations during infancy and childhood, characterized by a typical sequence of IgE antibody response and clinical symptoms.