

Natural History of Allergic Diseases and Asthma

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Outline

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

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 March(2)

- 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.

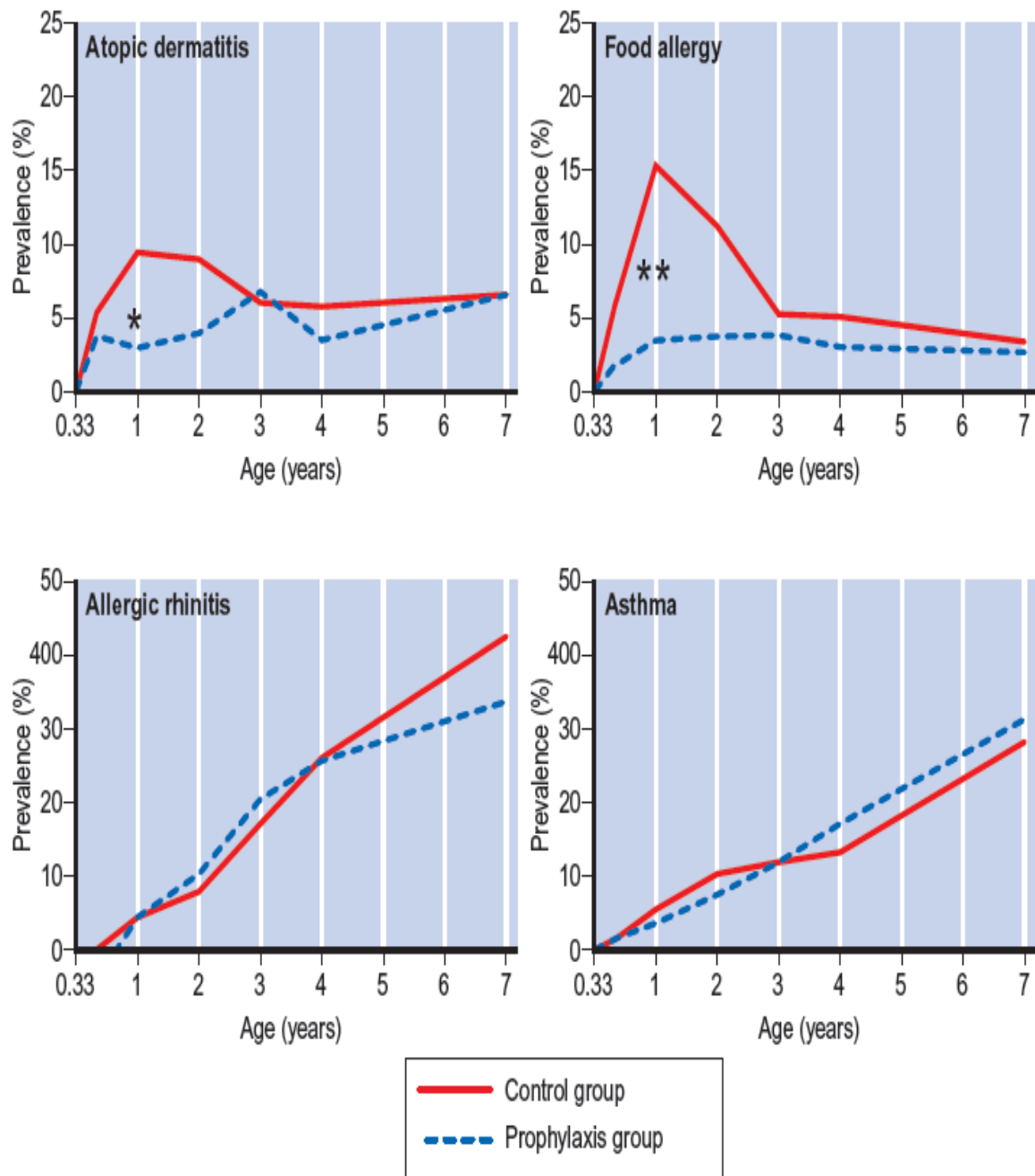


Figure 2-1 Allergic march of early childhood. Period prevalence of atopic dermatitis, food allergy, allergic rhinitis, and asthma from birth to 7 years in prophylactic-treated (allergenic food avoidance) and untreated (control) groups (Kaiser Permanente; San Diego). * $P \leq 0.05$; ** $P < 0.01$. (Data 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

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 usually 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

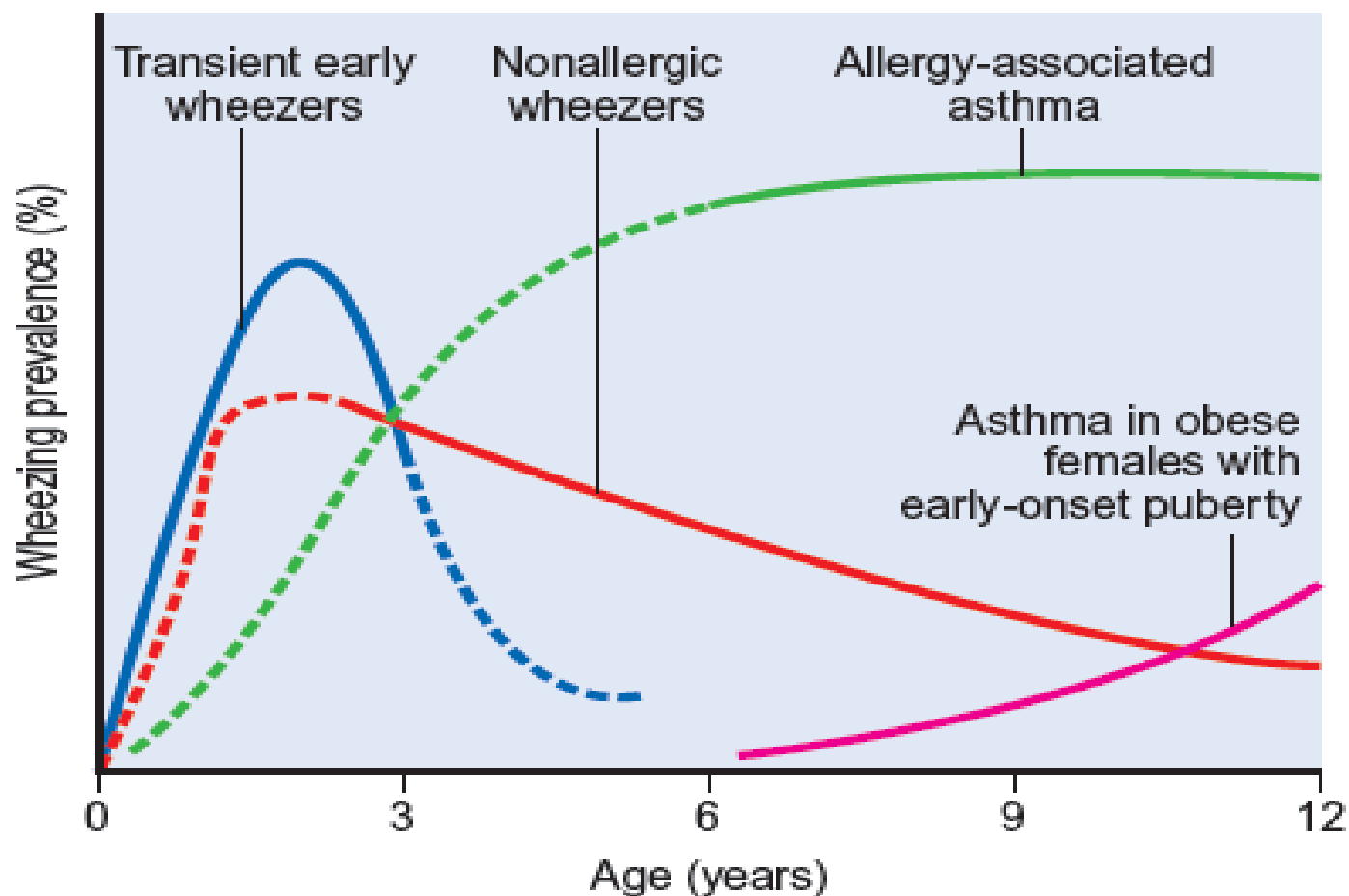


Figure 2-2 Hypothetical yearly prevalence for recurrent wheezing phenotypes in childhood (Tucson Children's Respiratory Study, Tucson, Arizona). This classification does not imply that the groups are exclusive. Dashed lines suggest that wheezing can be represented by different curve shapes resulting from many different factors, including overlap of groups. (Modified from Stein RT, Holberg CJ, Morgan WJ, et al. *Thorax* 1997;52:946–952.)

Tucson, CRS, study

Wheezing phenotype	Period of wheeze	N(%)	Recurrent wheeze/cough @16y(%)	LFTs 1y	LFTs 6y	LFTs 16y
Transient early	<3yrs	20	20	Lowest airflow	improved	Lower than normal
persistent	6rs	14	50	Normal	declined	Persist decline
Late onset	>3yrs	15	50			

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:

1 Major criterion	or 2 Minor criteria
Parental asthma	Allergic rhinitis
Eczema	Wheezing apart from colds
Inhalant allergen sensitization	Eosinophils $\geq 4\%$
	Food allergen sensitization

Figure 2-4 Modified Asthma Predictive Index for children (Tucson Children's Respiratory Study, Tucson, Arizona). Through a statistically optimized model for 2- to 3-year-old children with frequent wheezing in the past year, one major criterion or two minor criteria provided 77% positive predictive value and 97% specificity for persistent asthma in later childhood. (Adapted from from Castro-Rodriguez JA, Holberg CH, Wright AL, et al. *Am J Respir Crit Care* 2000;162:1403–1406; and Guilbert TW, Morgan WJ, Zeiger RS, et al. *J Allergy Clin Immunol* 2004;114:1282–1287.)

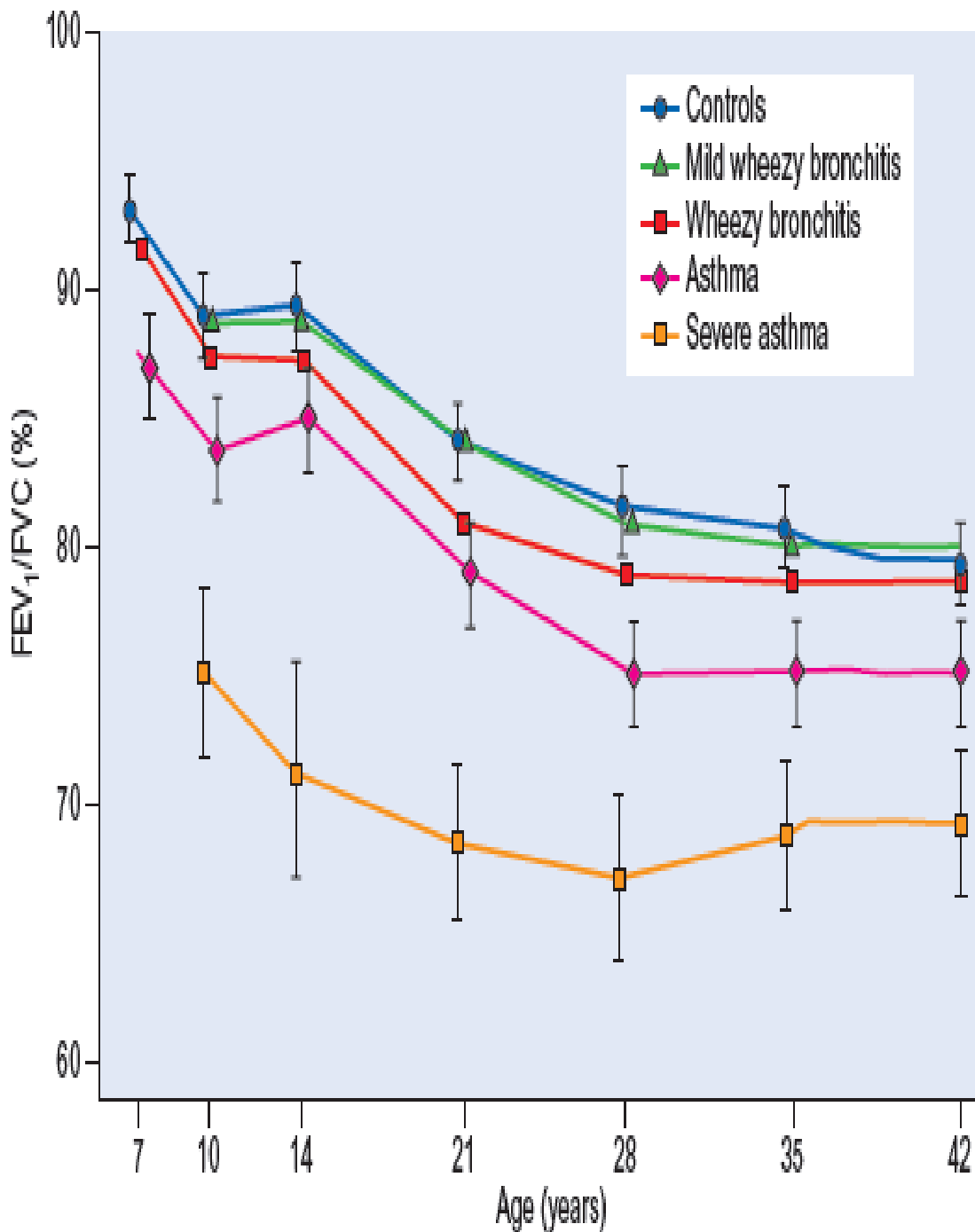


Figure 2-3 Natural history of lung function from childhood to adulthood (Melbourne Longitudinal Study of Asthma, Melbourne, Australia). Subjects were classified according to their diagnosis at time of enrollment: no-wheezing control; mild wheezy bronchitis; wheezy bronchitis; asthma; and severe asthma. 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 age 42 years from Horak E, Lanigan A, Roberts M, et al. *BMJ* 2003; 326(7386):422–423).

Atopic dermatitis (AD)

- Usual 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)

Initial examination			4 years later		
AD severity	Inhalant ± food	Food only	Inhalant ± food	Food only	Asthma and/or AR
Mild	15%	20%	31%	6%	15%
Moderate	18%	26%	52%	6%	32%
Severe	20%	45%	100%	0%	75%

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%)

Studies on challenge-proven food allergies in atopic dermatitis

Study (year)	location	No. of patients (mean age)	+ve SPT or Ig E	+ve food challenge
Burks et al (1988)	USA	165 (48 mnths)	60%+ve SPT	38.7%
Eigenmen et al (1988)	USA	63 (2.8yrs)	65% +ve IgE	37%
Eigenmen et al (2000)	Switzerland	74(2.5yrs)	59%+ve IgE	33.8%
Garcia (2007)	Spain	44(7.5 mnths)	61%+ve SPT/IgE	27%

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.

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