CME Questions

Q1. Results from which study types have challenged the concept a single allergic march sequence and instead support the existence of multiple allergic march trajectories?

A. Birth cohort studies

B. Latent class analyses

C. Animal models

D. A and B

E. A and C

Answer: D

Rationale:

The classical allergic march sequence of atopic dermatitis, asthma, and allergic rhinitis has been challenged by birth cohort studies and longitudinal latent class analyses.[1] A key study that demonstrated trajectory heterogeneity was performed by Belgrave *et al.* In this study Bayesian machine learning methods and latent class analysis identified multiple developmental profiles of atopic dermatitis, wheeze (a surrogate for asthma), and allergic rhinitis.[2] Only 7% of these profiles resembled the classical allergic march. In a separate study examining trajectories involving atopic dermatitis, asthma, and allergic rhinitis, Punekar *et al* observed 14 distinct allergic trajectories beyond the classical allergic march sequence.[3] While useful for the study of immunologic mechanisms that underlie the allergic march, animal (e.g. mouse) models are yet to be utilized to study allergic march trajectories.

References:

[1]Hill DA, *et al*. "A march by any other name." *Annals of Allergy, Asthma & Immunology* 121.1 (2018): 137-138.

[2]Belgrave DCM, *et al*. "Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies." *PLoS Med* 11.10 (2014): e1001748.

[3]Punekar YS and Sheikh A. "Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database." Clinical & Experimental Allergy 39.12 (2009): 1889-1895.

Q2. Which features of atopic dermatitis are most associated with increased risk for developing respiratory allergy later in life?

A. Early-onset, transient, moderate disease
B. Early-onset, transient, severe disease
C. Early-onset, persistent, severe disease
D. Late-onset, persistent, moderate disease
E. Late-onset, transient, severe disease

Answer: C

Rationale:

There is growing evidence that only certain subtypes, or endotypes, of atopic dermatitis are associated with progression of the allergic march.[1] In one prospective pediatric birth cohort study performed by Lowe *et al*, features of atopic dermatitis that significantly increased risk of asthma and allergic rhinitis included very early disease onset and

persistent disease.[2] In another study, early-onset and severe atopic dermatitis were associated with increased risk of sensitization to both food and aeroallergens.[3] Thus, from the available choices, early-onset, persistent, and severe atopic dermatitis is most associated with high risk for subsequent respiratory allergy.

References:

[1]Irvine AD and Mina-Osorio P. "Disease trajectories in childhood atopic dermatitis: an update and practitioner's guide." *British Journal of Dermatology* 181.5 (2019): 895-906.

[2]Lowe AJ, *et al*. "Age at onset and persistence of eczema are related to subsequent risk of asthma and hay fever from birth to 18 years of age." *Pediatric Allergy and Immunology* 28.4 (2017): 384-390.

[3]Gustafsson D, *et al*. "Development of allergies and asthma in infants and young children with atopic dermatitis–a prospective follow-up to 7 years of age." *Allergy* 55.3 (2000): 240-245.

Q3. Which of the following are functions associated with allergy susceptibility genes identified in genome-wide association studies?

A. Immune cell function
B. Cytokine signaling
C. Epithelial function

D. Gene regulation

E. All of the above

Answer: E

Rationale:

Multiple genome-wide association studies have revealed loci associated with increased susceptibility to allergic disease. Studies by Ferreira *et al* and Johansson *et al* collectively identified over 100 loci in association with the combined phenotype of AD, asthma, and/or allergic rhinitis.[1-3] Candidate susceptibility genes are thought to be essential for immune cell function and signaling, as well as epidermal differentiation. A number of intergenic variants have also been identified, which are suspected to have a gene regulatory role. Additional studies are needed to clarify the roles of genetic variants in predisposing to specific allergic trajectories.

References:

[1]Ferreira MA, *et al*. "Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology." *Nature Genetics* 49.12 (2017): 1752-1757.

[2]Ferreira MAR, *et al*. "Eleven loci with new reproducible genetic associations with allergic disease risk." *Journal of Allergy and Clinical Immunology* 143.2 (2019): 691-699.

[3]Johansson A, *et al*. "Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema." *Human Molecular Genetics* 28.23 (2019): 4022-4041.

Q4. The effects of differing farming practices on risk of developing childhood asthma and allergic sensitization were previously studied in the Amish and Hutterite populations that share genetic ancestry but differ in their farming practices. Which of the following are correctly paired?

A. Exposure to farm animals and reduced asthma risk
B. Elevated endotoxin level in house dust and increased asthma risk
C. Exposure to farm animals and increased allergic sensitization
D. Elevated endotoxin level in house dust and increased allergic sensitization
E. Exposure to farm animals and reduced endotoxin level in house dust

Answer: A

Rationale: Animal exposure in rural environments is associated with elevated endotoxin levels, lower risk of respiratory allergy, and reduced allergic sensitization.[1] The Amish and Hutterites represent genetically similar agricultural groups that differ in their farming practices; the Amish practice traditional farming while the Hutterites use industrialized farming. In a landmark study, children in the Amish population were exposed to higher house dust endotoxin levels and experienced lower rates of asthma and allergic sensitization.[2] The immunomodulatory property of endotoxin is an important aspect of

the hygiene hypothesis, which postulates that early-life exposures to microbes and their signals protect against the development of allergy.[3]

References:

[1]Peden DB. "The “envirome” and what the practitioner needs to know about it." *Annals of Allergy, Asthma & Immunology* 123.6 (2019): 542-549.

[2]Stein M, *et al*. "Innate immunity and asthma risk in Amish and Hutterite farm children." *New England Journal of Medicine* 375.5 (2016): 411-421.

[3]Ege MJ. "The hygiene hypothesis in the age of the microbiome." *Annals of the American Thoracic Society* 14.Supplement 5 (2017): S348-S353.

Q5. The parents of a boy with IgE-mediated food allergy, allergic rhinitis, and eosinophilic esophagitis are interested in learning about immunomodulatory therapies that might better control his various allergic manifestations. Which of the following would be a poor choice due to established associations with eosinophilic esophagitis?

A. Oral immunotherapy
B. Subcutaneous immunotherapy
C. Sublingual immunotherapy
D. A and B
E. A and C

Answer: E

Rationale:

Eosinophilic esophagitis (EoE) is a mixed IgE-mediated and non-IgE-mediated food allergy that is recently being recognized as a late manifestation of the allergic march.[1] Individuals with EoE have higher rates of IgE-mediated food allergy than the general population[1] and may experience exacerbation of disease during pollen season if they suffer from concurrent allergic rhinitis.[2] EoE is a known complication of oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) and as such these therapies are contraindicated in children with EoE. As subcutaneous immunotherapy (SCIT) does not involve enteral administration, EoE is not an expected side effect of this therapy.

References:

[1]Hill DA, *et al*. "Eosinophilic esophagitis is a late manifestation of the allergic march." *Journal of Allergy and Clinical Immunology: In Practice* 6.5 (2018): 1528-1533.

[2]Dowling PJ, *et al*. "The role of the environment in eosinophilic esophagitis." *Clinical reviews in Allergy and Immunology* 57.3 (2019): 330-339.

[3]Votto M, *et al*, "Eosinophilic gastrointestinal disorders and allergen immunotherapy: lights and shadows." *Pediatric Allergy and Immunology* (2021).