

Immunological Aspects of Allergy and Anaphylaxis

Although most of these children have respiratory problems, such as allergic rhinitis or bronchial asthma, many of those with allergies may also have atopic reactions to foods or medications. As antigens are slowly introduced into an infant's environment or diet, the child's propensity to deal with these new substances may not be developed. In addition, children's airways are small, their gastrointestinal tracts are not developed, and their immune systems are not ready to meet the challenges of these newly introduced proteins called *allergens*.

ALLERGIC HYPERSENSITIVITY

In 1964, Gell and Coombs classified four types of immunologically mediated hypersensitivity states. The majority of disease states encountered in the clinical practice of allergy are related to type I, or immediate type hypersensitivity. In this model, an allergen interacts with preformed IgE on the surface of a mast cell or basophil. This interaction causes cross-linking of the FcεRI receptor and release of multiple mediators, including histamine, leukotrienes, and various interleukins. Depending on the relative localization of release, clinical states such as allergic asthma, allergic rhinitis, or systemic anaphylaxis occur. Of the remaining clinical allergy hypersensitivity states, type IV, or delayed-type hypersensitivity, is most common. In this type, T-cell antigen receptors on TH1 or TH2 lymphocytes bind to tissue antigens, causing clonal expansion of lymphocytes and release of pro-inflammatory lymphokines. Distinct clinical entities such as contact dermatitis (e.g., poison ivy) or tuberculin skin test sensitivity in pulmonary tuberculosis may occur relative to the site of the tissue antigen.

Type	Mechanism	Responses
I	IgE mediated	Anaphylaxis, urticaria
II	Complement-mediated cytotoxicity	Cytopenias
III	Immune complex deposition	Vasculitis/ nephritis
IV	Delayed-type hypersensitivity	Dermatitis or hepatitis

ATOPY

Clinical allergic diseases are predominately type I, or IgE mediated. Approximately 40 percent of people in Western nations are inclined toward an exaggerated IgE response to multiple environmental allergens such as pollen or animal dander. This allergic state, known as atopy, is the result of multiple genetic and environmental factors. Our current understanding of the development of an IgE response favors a TH2 T-cell induction. When specific inhaled, ingested, or absorbed proteins, or allergens, appropriately stimulate this subset of the T-cell population, a series of cellular reactions occurs that leads to IgE antibody production. Inhalation of most proteins does not cause IgE-mediated responses, whereas a limited number of small protein allergens can elicit such reactions. Although the mechanism of allergic induction is not completely clear, some general principles have emerged. Allergens presented transmucosally at very low doses induce IgE responses by TH2 cells. This subset of cells produces the primary cytokines, interleukin-4 (IL-4) and interleukin-13 (IL-13). These interleukins interact with receptors on B lymphocyte cell surfaces, which promote class switching to the IgE antibody subclass. The subsequent class switch produces antigen-specific IgE antibodies with specificity toward common allergens such as pollen, animal dander, food, or venom. Although atopy has a strong genetic component, environmental factors best explain the recent global trend toward increased prevalence of allergic disease. Predictive factors include the following:

(1) decreased exposure to infectious disease during early childhood, (2) changes in diet, (3) higher levels of allergen exposure, and (4) increased environmental pollution.

SYSTEMIC ANAPHYLAXIS

Systemic anaphylaxis represents the clinical manifestation of type I hypersensitivity that occurs when a specific antigen and a homocytotropic antibody interact. The reaction can be sudden and progress rapidly, often without a clear cause. Clinically, these reactions lead to:

1. Airway and laryngeal edema and bronchospasm with potential for complete asphyxiation;
2. Gastrointestinal tract smooth muscle contraction, causing pain, vomiting, and diarrhea;
3. Blood vessel dilatation with potential for progression to circulatory collapse;
4. Cutaneous vascular permeability, resulting in flushing, urticaria, and angioedema.

Allergic Rhinitis

Is the most common allergic disease, It consists of two forms, seasonal and perennial. Seasonal allergic rhinitis is commonly referred to as “hay fever”

or “rose fever” and is triggered by pollens with a typically well-defined season of germination. Perennial allergic rhinitis has similar symptoms, yet involved substances are present year-round, including animal dander, dust mites, and mold.

Asthma

Asthma is a lower respiratory tract disease that is characterized by dyspnea and other symptoms including cough, chest tightness, chest pain, and wheezing. Persons with mild disease can often present only with a mild, chronic cough. In contrast to other obstructive lung diseases, asthma symptoms are characteristically relieved by bronchodilator and anti-inflammatory therapy. Respiratory viruses are the most frequently implicated causes of asthma attacks, especially in children, while tobacco smoke and air pollution are other major inciting agents. The majority of asthma patients are atopic, a term that reflects the production of IgE and both the genetic predisposition toward immediate type immune reactions and exposure to causative environmental agents such as pollens, dust mites, fungi, and many insects.

Systemic lupus erythematosus (SLE)

is a systemic autoimmune disease characterized by the production of autoantibodies and a diversity of clinical manifestations. It most commonly presents in women during their child-bearing years. Although the etiology of SLE is unknown, both genetic and environmental factors contribute to loss of self-tolerance. Current therapeutic modalities are anti-inflammatory and immunosuppressive.

Antinuclear antibodies (ANA)

are present in over 98% of patients diagnosed with SLE. Their presence is not specific to SLE as they are present in patients with other autoimmune diseases, malignancies, and viral (hepatitis) and parasitic (malaria) infections, as well as in response to environmental triggers such as therapeutic agents (see section on drug-induced lupus, below). Furthermore, ANA are found in low titer in 5% of the general population with prevalence increasing with age. Common ANA specificities found in lupus patients include dsDNA, ssDNA, extractable nuclear antigens.

Lupus nephritis

is an inflammation of the kidney caused by systemic lupus erythematosus (SLE), a disease of the immune system. Lupus nephritis results from the deposition of circulating immune complexes, which activate the complement cascade leading to complement-mediated damage, leukocyte infiltration, activation of procoagulant factors, and release of various cytokines. In situ immune complex formation following glomerular binding of nuclear antigens may also play a role in renal injury. The presence of antiphospholipid antibodies in patients.

TABLE 277-3 CLASSIFICATION FOR LUPUS NEPHRITIS

Class I	Minimal mesangial	Normal histology with mesangial deposits
Class II	Mesangial proliferation	Mesangial hypercellularity with expansion of the mesangial matrix
Class III	Focal nephritis	Focal endocapillary ± extracapillary proliferation with focal subendothelial immune deposits and mild mesangial expansion
Class IV	Diffuse nephritis	Diffuse endocapillary ± extracapillary proliferation with diffuse subendothelial immune deposits and mesangial alterations
Class V	Membranous nephritis	Thickened basement membranes with diffuse subepithelial immune deposits; may occur with Class III or IV lesions and is sometimes called mixed membranous and proliferative nephritis
Class VI	Sclerotic nephritis	Global sclerosis of nearly all glomerular capillaries