Immunoglobulin E

Importance in Parasitic Infections and Hypersensitivity Responses

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Immunoglobulin E (IgE) is one of the body's 5 classes (isotypes) of immunoglobulins (antibodies). Like other immunoglobulins, IgE is produced by B cells and plasma cells.[1,2] In contrast to other immunoglobulins, the concentration of IgE in the circulation is very low. Immunoglobulin E in cord blood usually measures less than 1 U/mL (1 U = 2.4 ng). Generally, adult IgE levels are achieved by 5 to 7 years of age. Between the ages of 10 and 14 years, IgE levels may be higher than those in adults. After age 70 years, IgE levels may decline slightly and be lower than the levels observed in adults younger than 40 years.

Circulating IgE concentrations are very low because mast cells have a very high affinity for IgE (10^{10} mol/L^{-1}) via their ϵ-heavy-chain Fc receptors (FcϵR). The synthetic rate for IgE is also very low. Immunoglobulin E attaches to mast cells and to basophils and activated eosinophils. Immunoglobulin E on mast cells has a half-life ($T_{½}$) of more than 10 days.

In contrast to other immunoglobulins that bind to immunoglobulin Fc receptors only when antigen has been bound by an antibody, IgE will bind to FcϵR in the absence of antibody. Immunoglobulin E binding to mast cells ''sensitizes'' the mast cells to degranulate when multivalent antigens cross-link FcϵR-bound IgE (Figure). Intrinsically innocuous antigens that produce hypersensitivity responses are termed *allergens.*

MAST CELL FUNCTION AND THE PROTECTIVE EFFECTS OF IgE

Mast cells play several roles in host defense. As the origin of many proinflammatory substances, mast cell degranulation–mediated inflammation allows circulating cells and plasma proteins increased access to interstitial spaces to combat infection. When antigens (or in the case of allergies, allergens) cross-link IgE on mast cell surfaces (eg, cause aggregation of IgE and FcϵR because the antigen is polyvalent, ie, expresses multiple identical epitopes), mast cell degranulation is triggered. Degranulation releases histamine and other biologic substances that can induce coughing, sneezing, vomiting, or diarrhea. These actions serve to expel pathogens from the body. Such pathogens include metazoan parasites. Parasites are classified as protozoans (single-cell parasites) or metazoans (multicell parasites). Parasitic infection can involve the gastrointestinal tract, lungs, blood stream, or solid organs. Metazoans are called helminths (worms). Elevated IgE levels occur in several helminthic infections. The helminths are divided into the flatworms (Platyhelminthes) and the roundworms (nematodes [Nemathelminthes]). The medically important flatworms are further divided into the flukes (Trematoda) and tapeworms (Cestoda). Tapeworms live in the gut but also can infect solid organs. Flukes live in the blood vessels, lungs, or liver. Examples of the consequences of parasitism include anemia, development of space-occupying lesions or granulomas in solid organs, allergic reactions, obstruction of blood vessels or lymphatics, induction of cancer, blindness, and diarrhea.

Immunoglobulin E also can induce an antibody-dependent, cell-mediated cytotoxic response against helminthic parasites. Immunoglobulin E that binds to such parasites focuses eosinophil targeting against the parasites. Once IgE is bound to the helminthic parasite and eosinophils bind to IgE, the eosinophil can degranulate against the parasite. Helminthic parasites are too large to be phagocytized. The toxic products of the eosinophil granules can either kill, damage, or dislodge the parasite as a protective host mechanism. Therefore, it is common to observe both elevated IgE levels and eosinophilia in many helminthic parasitic infections (see ''Differential Diagnosis of Elevated IgE Concentrations''). In summary, (1) IgE binds to the target parasite antigen, (2) the eosinophil FcRϵ receptor binds to Fcϵ of IgE, (3) the eosinophil degranulates toward the parasite, and (4) toxic products of the released eosinophil granules damage, destroy, or dislodge the parasite.

PATHOLOGIC EFFECTS OF IgE

In industrialized populations in which the frequency of helminthic parasitic infection is low, the adverse actions of IgE are manifested as a high frequency of type I hypersensitivity.[3,4] While allergy (hypersensitivity) was unusual at the turn of the century, allergies now affect up to 20% of adults. Approximately 5% of children have asthma, 15% of children have allergic rhinitis, 5% have eczema, and possibly up to 40% of all children are affected by minor allergic conditions. Experts hypothesize that the decreasing frequency of parasitism, which has occurred as a consequence of improved sanitation and hygiene, has left the immune system ''unoccupied,'' thereby fostering immune

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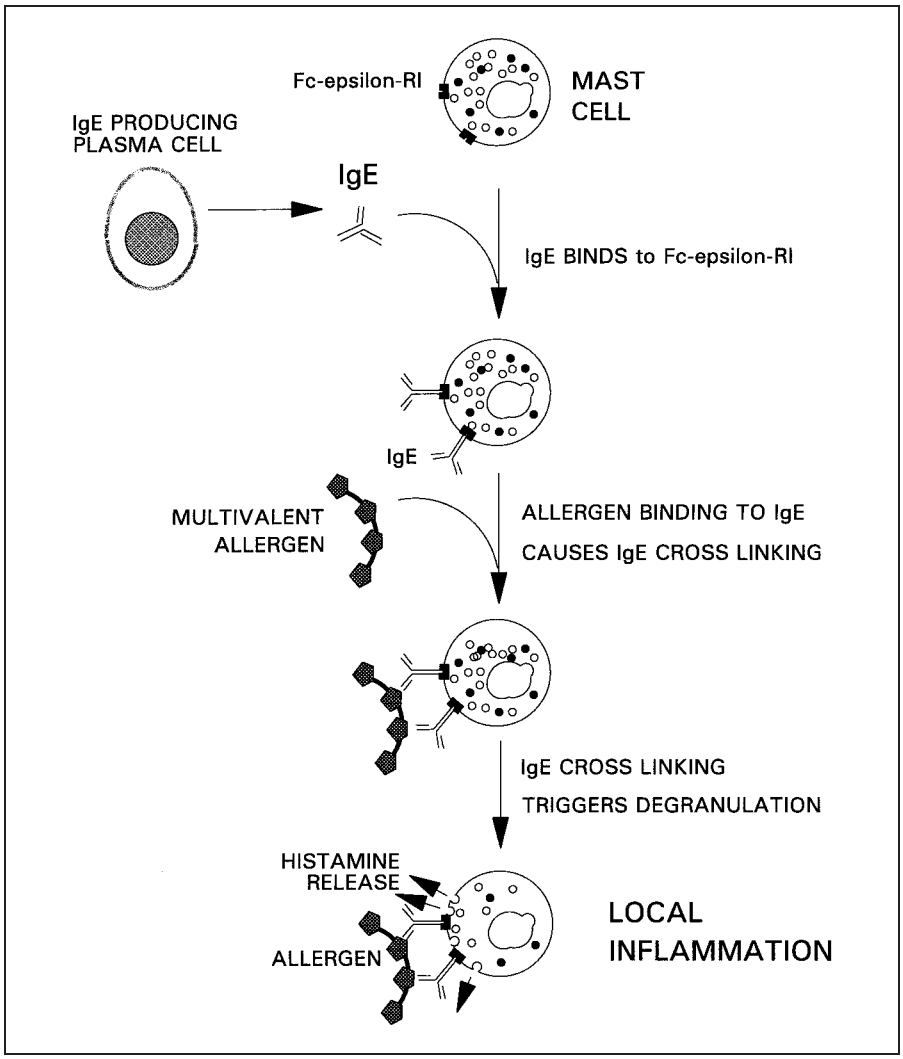

Type I hypersensitivity.

responses to benign antigens (eg, allergens) that produce allergic responses. Examples of type I hypersensitivity reactions are listed in Table 1.

DIFFERENTIAL DIAGNOSIS OF ELEVATED IgE CONCENTRATIONS

Circulating IgE levels are predominantly elevated in helminthic parasitic and allergic conditions. Table 2 provides a list of conditions in which elevated IgE levels may be found. As noted, in industrialized countries, allergy is the most common cause of elevated IgE concentrations, whereas in lesser developed, predominantly agrarian countries, parasitic infection is the most common cause of elevated IgE levels. Elevated IgE levels can be detected in some individuals before the expression of clinical allergy. However, the usefulness of such testing is unclear because no prophylactic immunotherapy exists to prevent the development of allergy.

While elevated IgE levels can be consistent with various allergic conditions, to determine the precise allergen to which an individual is sensitive, either radioallergosorbent testing (RAST) or skin testing should be carried out. Radioallergosorbent testing detects the presence of IgE sensitivity to specific allergens. Skin testing is performed by scratching or pricking the skin and applying a solution that contains a specific allergen over the abrasion. If the individual has mast cells under their skin sensitized with IgE specific for the allergen, an immediate hypersensitivity wheal and flare (eg, hive) response will develop within 15 to 20 minutes. Using skin testing, allergists can test for IgE antibody to 50 or more allergens simultaneously by applying multiple solutions to individual sites over the patient's back.

The advantage of RAST testing is that it can be performed simply by taking a blood specimen. However, in performing RAST testing for a large battery of allergens, the overall cost becomes substantial. Advantages of skin testing are that (1) skin testing more closely relates to clinical disease than RAST testing and (2) since an allergist performs the testing in a clinic, the results are available immediately.

IgE DEFICIENCY

It is difficult to define IgE deficiency because IgE levels are normally very low. Immunoglobulin E deficiency can be defined as IgE levels less than 2 U/mL in children and less than 4 U/mL in adults. Low IgE levels have been reported in various forms of severe combined immunodeficiency, hyper-IgM syndrome, ataxia telangiectasia, X-linked recessive Bruton agammaglobulinemia, common

Table 1. Clinical Examples of Type I Hypersensitivity Disorders

Disorder	Clinical Manifestations	Allergens	Route of Exposure
Systemic anaphylaxis	Edema, vasodilation, tracheal mucosal swelling with occlusion, circulatory collapse, death	Drugs, serum, venoms	Intravenous
Wheal and flare responses	Local vasodilation and edema	Insect bites, allergy testing	Subcutaneous
Allergic rhinitis (hay fever)	Edema and irritation of nasal mucosa	Pollens (ragweed, timothy, birch), mite feces	Inhalation
Bronchial asthma	Bronchial constriction, mucosal edema from inflammation, excessive mucus production	Pollens, dust mite feces	Inhalation
Food allergy	Vomiting, diarrhea; pruritus, urticaria (hives: allergen travels to skin)	Shellfish, milk, fish, wheat, legumes, corn, citrus fruit, eggs, tomatoes	Oral

Table 2. Differential Diagnosis of Elevated Immunoglobulin E (IgE)

Category	Examples
Allergic disease	Atopic dermatitis (eczema)
	Allergic rhinitis
	Allergic asthma
	Extrinsic allergic alveolitis
	Drug allergies
	Allergic urticaria
Parasitic disease	
Cestodes	*Echinococcus granulosus*
	Echinococcus multiocularis
Trematodes	*Schistosoma mansoni*
	Schistosoma japonicum
	Schistosoma haematobium
Nematodes	*Ascaris lumbricoides*
	Ancylostoma caninum
	Ancylostoma braziliense
	Capillaria philippinensis
	Toxocara canis
	Toxocara cati
Immunologic disorders	
Monoclonal gammopathy	IgE monoclonal gammopathy
Immune deficiency states	Hyper-IgE syndrome
	Wiskott-Aldrich syndrome
	DiGeorge syndrome
	Nezelof syndrome
	Graft versus host disease
	Acquired immunodeficiency syndrome
	Cystic fibrosis
Inflammatory diseases	Kawasaki disease
	Periarteritis nodosa
Infectious diseases	Leprosy
	Bronchopulmonary aspergillosis
	Aspergilloma

Table 3. Clinial Use of Immunoglobulin E (IgE) Measurements

Measurement of IgE *always* indicated in patients with suspected
- IgE monoclonal gammopathy
- Hyper-IgE syndrome
- Allergic bronchopulmonary aspergillosis
- Immunodeficiency syndromes

Measurement of IgE *sometimes* indicated in patients with suspected
- Allergic disease
- Helminthic parasitism

Measurement of IgE *usually not* indicated in patients with suspected
- Inflammatory diseases
- Nonparasitic infectious diseases

variable immunodeficiency, transient hypogammaglobulinemia of infancy, and isolated IgE deficiency whose clinical significance is unclear. Some experts in immunodeficiency diseases recommend that IgE be measured if an antibody deficiency state is being considered.

ANALYTICAL ISSUES IN THE MEASUREMENT OF IgE

Solid-phase displacement radioimmunoassays, double-antibody radioimmunoassays, solid-phase sandwich radioimmunoassays, and nephelometry are all used to measure IgE. In most assays, the lower limit of detection is 0.5 U/mL (1.2 ng/mL). According to the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88), acceptable control ranges are within ±3 SD of the mean control value. The overall precision goal should be ±0.75 SD of the mean. The maximum total error (fixed limit goal) according to CLIA '88 is ±3 SD of the mean.

CLINICAL USE OF IgE MEASUREMENTS

The suggested clinical application of IgE measurements is outlined in Table 3. An elevated IgE concentration is not diagnostic of any single condition. However, there are at least 3 conditions (IgE monoclonal gammopathy, hyper-IgE syndrome, and allergic bronchopulmonary aspergillosis) in which elevated IgE levels are universally observed. A normal IgE level excludes an IgE monoclonal gammopathy, hyper-IgE syndrome, and allergic bronchopulmonary aspergillosis. Depressed or elevated IgE levels are sought frequently in suspected immunodeficiency disorders.

An elevated IgE concentration frequently is found in various allergic and helminthic parasitic diseases, as outlined in Table 2. An elevated IgE level would support the diagnosis of an allergic or helminthic parasitic disorder, but a normal IgE concentration would not exclude the specific diagnosis under consideration. If the diagnosis of allergy or helminthic parasitism is unclear, an otherwise unexplained elevated IgE value may be helpful in suggesting allergy or parasitism. However, if the diagnosis of allergic or helminthic parasitic disease is likely, measurement of IgE is not likely to provide substantial additional information.

In infants, IgE levels greater than 20 U/mL support the diagnosis of allergic rhinitis; however, a normal IgE value does not rule out allergic conditions. Immunoglobulin E levels in adults are less helpful in establishing an allergic etiology for symptoms. In patients with suspected allergic conditions, IgE levels greater than +1 SD above the mean ''suggest'' allergic disease, while values greater than +2

SD above the mean ''strongly suggest'' allergic disease. Measuring the total IgE concentration is not usually helpful once the diagnosis of allergic disease has been established clinically, whereas an elevated IgE value has only limited power in predicting allergic tendencies. Therefore, measuring IgE in the latter 2 situations is not recommended.

Finally, elevated IgE levels are observed in many inflammatory and infectious diseases. Immunoglobulin E measurements are usually not helpful in such conditions, and IgE measurements are rarely indicated.

SUMMARY

Compared with the major circulating immunoglobulins (IgG, IgA, and IgM), IgE normally occurs in very low concentrations in the circulation. The normal concentration of IgE is only 0.05% of the IgG concentration. Because immunoassay procedures are necessary to measure the low circulating concentrations of IgE, IgE proficiency testing is included in the general ligand surveys of the College of American Pathologists (K, KN [K with SI unit reporting], and KK [K with a duplicate set of vials]). This review of IgE focused on the biology of IgE, the differential diagnosis of elevated IgE concentrations, the measurement of IgE, and the clinical indications for the measurement of IgE.

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