

Evaluation and clinical interpretation of hypergammaglobulinemia E: differentiating atopy from immunodeficiency

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INTRODUCTION

Total serum IgE levels are elevated in a broad array of clinical settings, including infectious, oncologic, inflammatory, allergic, and primary immunodeficiency disorders. It is neither a sensitive nor a specific diagnostic marker for any given disease. This article discusses the laboratory quantitation and clinical interpretation of total IgE levels, with emphasis on differentiating atopy from underlying primary immunodeficiency as the cause of hypergammaglobulinemia E states.

ASSAY METHODS

Total serum IgE levels can be quantitated by means of nephelometry (eg, N Latex IgE mono; Dade-Behring, Marburg, Germany) or solid-phase sandwich immunoassay using either a cellulose-polymer sponge (eg, ImmunoCAP InVivoSight; Phadia AB, Uppsala, Sweden) or a paper disk (eg, enzyme immunoassay) (Hycor Biomedical, Garden Grove, California). The principles of nephelometry have recently been reviewed.¹ Solid-phase sandwich immunoassays use an anti-human IgE antibody bound to a solid substrate to capture IgE in a sample. After washing away unbound protein, a secondary anti-IgE antibody labeled with an enzyme is then added. Detection is accomplished by the addition of enzyme substrate, producing a colorimetric, chemiluminescent, or fluorescent reaction that can be quantitatively measured and compared with a calibrated standard. This standard is derived from the World Health Organization Second International Reference Preparation 72/502, established in 1981. Under this standard, 1 mass unit (1 IU) is equal to 2.4 ng of IgE.²

Reference values vary by age and assay method; thus, readers should refer to the reference values provided by their clinical laboratory. Several practical observations can be made: (1) unlike IgG, IgE does not cross the placenta; (2)

total IgE is generally undetectable at birth, rises during childhood, and reaches adult levels in early adolescence; (3) at any given age there is a considerable range for what is "normal"; and (4) in serum, total IgE in the reference range of 0 to 500 ng/mL is approximately 10,000-fold less abundant than total IgG, which is typically present in the range of 500 to 1,500 mg/dL.¹ Despite its relative scarcity, IgE exhibits profound bioactivity in vivo owing to its interaction with high-affinity FcεRI cell surface receptors on mast cells and basophils and its ability to up-regulate expression of these high-affinity receptors.

INFECTIOUS CAUSES

In developing countries, parasitic infections, rather than atopy, commonly cause elevations in IgE levels. Although filaria and *Schistosoma* are not endemic to the United States, *Toxocara*, *Strongyloides*, *Trichuris*, *Ascaris*, *Echinococcus*, and hookworms should be considered. Laboratory evaluation may reveal eosinophilia and increased IgE levels, although usually less than 1,000 IU/mL. Nonparasitic infections are also associated with elevated IgE levels, including *Mycobacterium tuberculosis*, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus.

ONCOLOGIC CAUSES

Monoclonal/oligoclonal elevations in total IgE levels may result from gammopathies or paraneoplastic syndromes. Benign monoclonal IgE gammopathy has been described once, and IgE multiple myeloma is rare (0.01% of plasmacytomas).^{3,4} Both can be recognized using protein electrophoresis and immunofixation. Cutaneous T-cell lymphoma/Sézary syndrome, Hodgkin disease, and non-Hodgkin lymphoma can be associated with elevated IgE levels.

INFLAMMATORY CAUSES

Several inflammatory conditions are associated with increases in total IgE levels. Kimura disease is a rare, benign inflammatory disease most frequently affecting Asian men in the third decade of life. Presenting symptoms include regional lymphadenopathy and adenitis of the face and neck. Laboratory studies reveal peripheral eosinophilia, elevated total IgE levels typically greater than 1,000 IU/mL, and

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reticular IgE deposition in lymph node germinal centers.⁵ Churg-Strauss syndrome features extravascular granulomatosis, eosinophilic vasculitis of small and medium-sized vessels, severe peripheral eosinophilia, and elevated IgE levels usually up to 5,000 IU/mL.⁶ Variable increases in serum IgE levels have also been observed after bone marrow transplantation, with or without acute graft-vs-host disease.⁷

ALLERGIC CAUSES

Atopy is the most frequent cause of increased total IgE values in developed nations. Because allergists are intimately familiar with these disorders, they are mentioned only briefly herein. In atopic dermatitis, IgE levels may be elevated, even to more than 10,000 IU/mL.⁸ There is increased susceptibility to cutaneous infections. However, invasive infections are rare in atopic dermatitis and should prompt an evaluation for immunodeficiency. Increased IgE levels also correlate with airway hyperresponsiveness, asthma, allergic rhinitis, food and drug hypersensitivity, allergic fungal sinusitis, and allergic bronchopulmonary aspergillosis.^{9,10} Unlike most diseases, in allergic bronchopulmonary aspergillosis, total IgE concentration is valuable as a diagnostic criterion (>400 IU/mL) and for therapeutic monitoring.¹¹

PRIMARY IMMUNODEFICIENCY CAUSES

Several primary immunodeficiency disorders are associated with elevated total IgE levels. The prototypic example is the rare hyper-IgE syndrome (HIES), also known as Job syndrome. This syndrome is characterized by recurrent staphylococcal abscesses of the skin and viscera, recurrent pneumonias with development of pneumatoceles or bronchiectasis, eosinophilia, and elevations in IgE levels that may range from 2,000 to greater than 50,000 IU/mL. Eczema, mucocutaneous candidiasis, retention of primary teeth, coarse facial features, osteopenia with pathologic fractures, hyperextensible joints, and increased risk of malignancy are additional features. As with atopic dermatitis, antistaphylococcal IgE can be detected in patients with HIES, but it is a nonspecific finding.¹² However, the contribution of these specific antibodies to HIES pathogenesis is presently unclear. The presence of parenchymal lung abnormalities, recurrent fungal infections, and deep-seated infections distinguish HIES from classic atopy. The presence of peripheral blood eosinophilia and increased serum IgE levels are supportive but are neither diagnostic nor specific for HIES. Computed tomography of the chest may demonstrate parenchymal lung changes, spinal films may demonstrate scoliosis, and a bone density scan or skeletal survey may reveal osteopenia and previous fractures. Ultimately, the diagnosis of HIES has been a clinical one made across time as patients accrue additional features suggestive of this disorder. A scoring system has been established, and it is a useful tool for evaluating patients with suspected HIES (Table 1).¹³ Most HIES is sporadic; however, autosomal dominant and recessive forms have been reported. Dominant-negative mutations in the transcription factor STAT3 are found in sporadic HIES,

and a mutation in the tyrosine kinase Tyk2 may be associated with some autosomal recessive HIES.^{14–17} Thus, genetic testing is now a means for establishing a definitive diagnosis. This should remove much of the historical uncertainty surrounding the diagnosis of HIES.

Wiskott-Aldrich syndrome is a rare, X-linked syndrome due to mutations in Wiskott-Aldrich syndrome protein, a regulator of actin polymerization and cytoskeletal reorganization. Microcytic thrombocytopenia, eczema, and recurrent infection form the classic presenting triad. Eczema may be localized and mild or generalized and severe and may be accompanied by food or drug allergies. Infections include complicated otitis media, pneumonia, sinusitis, meningitis, and sepsis, with increased susceptibility to herpes simplex, varicella, and *Pneumocystis jiroveci*. Dysregulated immunity may lead to vasculitis, inflammatory bowel disease, and lymphoproliferative malignancies. Laboratory studies frequently reveal elevated IgE (up to 5,000 IU/mL) and IgA levels, normal IgG levels, and low IgM levels. Specific antibody responses to polysaccharide and protein antigens and to isohemagglutinins are impaired. Lymphopenia and diminished T-cell functions and natural killer cell cytolytic activity are also observed.¹⁸

DiGeorge syndrome is a varying constellation of thymic hypoplasia, parathyroid hypoplasia, conotruncal cardiac defects, cleft palate, velopharyngeal insufficiency, and characteristic facies. Most, but not all, patients have a heterozygous deletion in chromosome 22q11. There is variable deficiency in T-cell numbers and function. Increased IgE levels have been found in some patients with partial DiGeorge syndrome.¹⁹

Netherton syndrome is a rare, autosomal recessive disease caused by mutations in SPINK5, a serine protease inhibitor. Features include trichorrhexis invaginata, ichthyosis, atopy, immunodeficiency, eosinophilia, and elevated IgE levels ranging from 100 to greater than 10,000 IU/mL. Recurrent or severe skin, respiratory tract, and systemic infections occur and may be related to depressed IgG levels.²⁰ The characteristic bamboo hair and skin manifestations help distinguish Netherton syndrome from HIES.

Elevations in IgE levels have been described in other primary immunodeficiency disorders. Omenn syndrome occurs in the context of T⁺B⁺ severe combined immunodeficiency. Hypomorphic mutations in *RAG1*, *RAG2*, or *ARTEMIS* genes allow for leaky T-cell receptor rearrangement, resulting in an oligoclonal T-cell population skewed toward autoreactivity. Consequently, a graft-vs-host disease–like reaction is observed shortly after birth. Generalized exudative erythroderma with desquamation, lymphadenopathy, and hepatosplenomegaly are seen along with severe respiratory tract infections, intractable diarrhea, and failure to thrive. Laboratory studies demonstrate eosinophilia, hypogammaglobulinemia, and elevated IgE levels up to 45,000 IU/mL. Lymphopenia is rare, but T cells express activation and memory markers, such as CD25 and CD45RO.²¹ Maternal engraftment of alloreactive T cells in the setting of severe

Table 1. Clinical Scoring System for Hyper-IgE Syndrome^a

Clinical features	Points ^b									
	0	1	2	3	4	5	6	7	8	10
Highest IgE level, IU/mL	<200	200–500			501–1,000				1,001–2,000	>2,000
Skin abscesses, No.	0		1–2		3–4				>4	
Pneumonia (lifetime), No.	0		1		2		3		>3	
Parenchymal lung abnormalities	None						Bronchiectasis		Pneumatocele	
Retained primary teeth, No.	0	1	2		3				>3	
Scoliosis, maximum curvature, Degrees	<10		10–14		15–20				>20	
Pathologic fractures, No.	0				1–2				>2	
Highest eosinophil count, cells/ μ L	<700			700–800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst)	Absent	Mild	Moderate		Severe					
Upper respiratory tract infections per year, No.	1–2	3	4–6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width, SD	<1	1–2		>2						
High-arched palate	Absent		Present							
Young-age correction, y	>5			>2–5		>1–2		$\leq$ 1		

^a Adapted from Grimbacher et al.¹³^b All patients in the initial series describing the STAT3 mutation in hyper-IgE syndrome scored 40 or higher.¹⁴

combined immunodeficiency is clinically similar. Other rare combined immunodeficiencies without a molecular etiology have also been associated with increases in total IgE levels, such as the diagnosis historically referred to as “Nezelof syndrome.”²²

SUMMARY

Increases in total serum IgE levels can be observed in many diverse conditions, from infection to atopy to primary immunodeficiency. The differentiation of atopy from immunodeficiency most often is made on a clinical basis, after taking findings from history, physical examination, and laboratory studies into consideration. However, total IgE level is neither a sensitive nor a specific diagnostic marker for any particular disease and, therefore, should not be relied on to establish a diagnosis of either atopy or primary immunodeficiency.

REFERENCES

- Agarwal S, Cunningham-Rundles C. Assessment and clinical interpretation of reduced IgG values. *Ann Allergy Asthma Immunol.* 2007;99:281–283.
- Bazal M, Hamburger RN. Standardization and stability of immunoglobulin E (IgE). *J Allergy Clin Immunol.* 1972;49:189–191.
- Ludwig H, Vormittag W. “Benign” monoclonal IgE gammopathy. *BMJ.* 1980;281:539–540.
- Kairemo KJ, Lindberg M, Prytz M. IgE myeloma: a case presentation and a review of the literature. *Scand J Clin Lab Invest.* 1999;59:451–456.
- Abuel-Haija M, Hurford MT. Kimura disease. *Arch Pathol Lab Med.* 2007;131:650–651.
- Weller PF, Plaut M, Taggart V, Trontell A. The relationship of asthma therapy and Churg-Strauss syndrome: NIH workshop summary report. *J Allergy Clin Immunol.* 2001;108:175–183.
- Ringden O, Persson U, Johansson SG, et al. Markedly elevated serum IgE levels following allogeneic and syngeneic bone marrow transplantation. *Blood.* 1983;61:1190–1195.
- Stone SP, Muller SA, Gleich GJ. IgE levels in atopic dermatitis. *Arch Dermatol.* 1973;108:806–811.
- Sears MR, Burrows B, Flannery EM, et al. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med.* 1991;325:1067–1071.
- Wittig HJ, Belloit J, De Fillippi I, Royal G. Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease. *J Allergy Clin Immunol.* 1980;66:305–313.
- Ricketti AJ, Greenberger PA, Patterson R. Serum IgE as an important aid in management of allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol.* 1984;74:68–71.
- Walsh GA, Richards KL, Douglas SD, Blumenthal MN. Immunoglobulin E anti-*Staphylococcus aureus* antibodies in atopic patients. *J Clin Microbiol.* 1981;13:1046–1048.
- Grimbacher B, Schaffer AA, Holland SM, et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. *Am J Hum Genet.* 1999;65:735–744.
- Minegishi Y, Saito M, Tsuchiya S, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature.* 2007;448:1058–1062.

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15. Minegishi Y, Saito M, Morio T, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity*. 2006;25:745–755.
16. Woellner C, Schaffer AA, Puck JM, et al. The hyper IgE syndrome and mutations in TYK2. *Immunity*. 2007;26:535.
17. Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007;357:1608–1619.
18. Orange JS, Stone KD, Turvey SE, Krzewski K. The Wiskott-Aldrich syndrome. *Cell Mol Life Sci*. 2004;61:2361–2385.
19. Grimbacher B, Belohradsky BH, Holland SM. Immunoglobulin E in primary immunodeficiency diseases. *Allergy*. 2002;57:995–1007.
20. Sprecher E, Chavanas S, DiGiovanna JJ, et al. The spectrum of pathogenic mutations in SPINK5 in 19 families with Netherton syndrome: implications for mutation detection and first case of prenatal diagnosis. *J Invest Dermatol*. 2001;117:179–187.
21. Honig M, Schwarz K. Omenn syndrome: a lack of tolerance on the background of deficient lymphocyte development and maturation. *Curr Opin Rheumatol*. 2006;18:383–388.
22. Buckley RH, Fiscus SA. Serum IgD and IgE concentrations in immunodeficiency diseases. *J Clin Invest*. 1975;55:157–165.
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