

Review article

Immunoglobulin E in primary immunodeficiency diseases

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Immunoglobulin E (IgE) was discovered in the late 1960s (1,2). Since then, aberrations of IgE synthesis have been noted in allergic diseases, in certain bacterial, fungal and parasitic infections, in graft-versus-host disease, and in certain acquired and primary immunodeficiency disorders (PID). However, the exact biological role of IgE under these conditions is unclear. This review will focus on IgE abnormalities in PID in which either deficiency or excess of IgE production is associated with increased susceptibility to infection. Particular emphasis will be put on the hyper-IgE syndrome, the Wiskott–Aldrich syndrome, the Omenn syndrome and the Comèl–Netherton syndrome (Table 1).

Immunoglobulin E

At birth, serum levels of IgE are usually undetectable, rising to 8–200 IU/ml in healthy nonatopic children during the first 5 years of life (3). In childhood, IgE levels depend on factors such as age and genetic background, as well as environmental factors including allergen exposure and parasitic diseases. IgE has a very short half-life, less than 1 day, and is present in lower concentrations in serum than any other immunoglobulin. Despite the low blood levels, IgE is extremely biologically active. This is because IgE

binds to high-affinity receptors on the surface of mast cells and basophils, making these cells highly sensitive to stimulation by IgE antibody–allergen interaction. This reaction is the key to IgE-mediated allergy (4). Moreover, the expression of these high-affinity receptors is probably up-regulated by IgE itself (5, 6, 7). Therefore, the concentration of circulating IgE does not reflect its true activity.

T cells play an important role in immune and inflammatory pathways. CD4⁺ T cells regulate or organize most types of immune responses to foreign proteins by secreting cytokines such as interleukins and interferons; they can be categorized as Th0, Th1, and Th2 cells on the basis of their products. Th1 cells are primarily involved in classic delayed hypersensitivity and have been proposed to inhibit Th2-driven processes. In contrast, the Th2 class releases primarily IL-4 and IL-5, and to some extent IL-13, which induce the Ig switch to IgE production, stimulate eosinophilopoiesis, regulate eosinophil functions, and promote the growth of mucosal-type mast cells, thus enabling immediate allergic response. The so called “switch factor” IL-4 has a wide variety of functions, including up-regulation of cell-surface major histocompatibility complex (MHC) class II molecules and CD23, the low affinity IgE receptor, and promotion of the growth of T and B cells, and mast cells (8). IL-13 also

Table 1. IgE abnormalities in which either deficiency or excess of IgE production is associated with increased susceptibility to infection

Disorder	Incidence	Genetic defect	Range of IgE peak levels U/ml	Cutaneous findings
Hyper-IgE syndrome (HIES)	About 200 cases published	Unknown	1 875 up to > 80 000	AEDS, impetigo, abscesses, candidiasis
Wiskott-Aldrich syndrome (WAS)	1 : 250 000	WAS gene	Normal up to 5 000	AEDS, petechiae, hematoma
Omenn syndrome (OS)	41 cases published (121)	RAG 1 or RAG 2	Normal up to 45 000	Congenital erythroderma
Comèl-Netherton syndrome (NS)	21 cases published (133)	SPINK 5	Normal up to > 10 000	Congenital erythroderma, ichthyosis, AEDS

causes B cells to isotype-switch for IgE production independent of IL-4 (9, 10, 11).

Disorders characterized by defective IgE production

It is difficult to define IgE deficiency, since in most routine laboratories normal values range from 0 to about 200 IU/ml. In 1970, Levy and Chen encountered an IgE-deficient person who was apparently healthy (12). Immunoglobulin deficiency, including IgE deficiency can be found in transient hypogammaglobulinemia of infancy, common variable immunodeficiency, X-linked agammaglobulinemia, X-linked immunodeficiency with hyper-IgM, severe combined immunodeficiency disease, and ataxia-telangiectasia. In all of these diseases, IgE deficiency is accompanied by a profound deficiency in IgG production. The latter is most likely responsible for the increased susceptibility to infections, since therapy with intravenous IgG, which contains no IgE, helps to reduce substantially the morbidity (13).

The biological need for IgE antibodies is still debated. It has been proposed that resistance to parasitic infections is mediated by chemotactic factors for eosinophils produced by IgE-sensitized mast cells. These factors include histamine, eosinophilic chemotactic factors, platelet activating factor, and leukotriene B₂. The eosinophils attracted by this are capable of killing schistosomula of *Schistosoma mansoni* by both IgE- and IgG-dependent, as well as complement-dependent, mechanisms (14, 15). However, the precise mechanism(s) of killing have not been established. In 1977, Juhlin and Michaelsson (16) reported a man in whom eosinophils and basophils were absent. He had a lifelong history of repeated otitis, sinusitis, and pneumonia. As an adult, he had numerous warts and chronic scabies.

Disorders characterized by excessive IgE production

The definition of excessive IgE production varies. IgE is one of a handful of laboratory values with a logarithmic range. Monoclonal production of IgE is rarely found in plasmocytoma and has not been reported in children (17). Polyclonal increases of serum IgE in developed countries

are most frequently caused by an allergen-specific IgE antibody response, as in atopic eczema/dermatitis syndrome (AEDS) (18). In AEDS, IgE levels are usually around 1000 IU/ml, but may be as high as 10 000 IU/ml. In undeveloped countries polyclonal IgE elevation is commonly due to parasitic infections. IgE levels in patients with parasites exceed 1000 IU/ml in only exceptionally rare cases. However, polyclonal IgE elevations can also be seen after viral infections such as cytomegalovirus (CMV) (19), intrauterine infections (20), "chemical" stimulation from substances like cigarette smoke (21), or major immunologic events like bone-marrow transplantation and graft-versus-host disease (GVHD) (22). The pathophysiology by which excessive production of IgE might adversely affect host defence is not known. One hypothesis is that with an underlying partial T cell deficiency, patients may have increased Th2 cells or cytokines, or a deficiency of Th1 type cells or cytokines, driving B cells to isotype-switch for IgE production via IL-4 (8, 23, 24). This might explain both the infection susceptibility and the augmented production of IgE.

In DiGeorge syndrome (chromosome 22q11.2 deletion syndrome) (25), which is characterized by thymic hypoplasia, meta-analyses of small cohorts revealed elevated serum IgE in 11 out of 35 patients (26–30). Allergic signs or symptoms, however, were not common in these infants. Elevated serum IgE concentrations may be related to the degree of thymic hypoplasia. Patients with complete DiGeorge anomaly may not have sufficient T-helper cell function to initiate IgE formation. On the other hand, those with the more common partial form of DiGeorge anomaly (31), who have some T cell function, may be more likely to have increased IgE production because they may have sufficient Th2-type cells or cytokines but a deficiency of Th1-type cells or cytokines.

Another characteristic shared by many patients with immunodeficiency who have elevated IgE levels is a tendency to be infected with staphylococci. This raises the issue of whether excessive IgE levels are permissive for *Staphylococcus aureus* infections, or whether staphylococcal infections stimulate excessive production of IgE. The latter is contradicted by the fact that most patients

with chronic granulomatous disease or with cystic fibrosis have relatively normal IgE concentrations, despite frequent staphylococcal infections (32; and Holland, unpublished data).

The hyperimmunoglobulin-E recurrent infection syndrome

“So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown.” From this citation (*Job II:7*) Davis, Schaller and Wedgewood coined the term Job’s syndrome in 1966 (33). They described two red-haired, fair-skinned girls who had frequent sinopulmonary infections, severe dermatitis, and recurrent staphylococcal skin infections that were remarkable for their lack of surrounding warmth, erythema, or tenderness.

The syndrome was further defined and clarified by Buckley et al. in 1972 (34) who noted similar infectious problems in two boys with severe dermatitis, characteristic facies, and elevated IgE levels, leading to the term Buckley syndrome. Following this report, elevated levels of IgE and a defect in neutrophil chemotaxis were identified in the two girls from the initial report showing that Job’s syndrome and Buckley syndrome represented the same condition (35). To avoid further confusion, the name “hyperimmunoglobulin E recurrent infection syndrome” (HIE or HIES) is now widely accepted. In 1999, our group at the National Institutes of Health further defined the phenotype of HIES. The incidence of 20 clinical features associated with HIES was published, based on a cohort of 30 patients with clear-cut HIES (36). It became clear that the hyper-IgE recurrent infection syndrome (Online Mendelian Inheritance in Man (OMIM) database #147060, #243700) is a rare primary immunodeficiency characterized by recurrent staphylococcal skin abscesses, pneumonias with pneumatocele formation, extreme elevations of serum IgE, eosinophilia, and distinct abnormalities of the connective tissue, skeleton, and dentition (33–39). Most cases are sporadic. However, there have been reports of autosomal dominant kindreds (36, 39–45) and autosomal recessive inheritance in consanguineous families (Renner et al. submitted).

Eczema, abscesses, pneumonia, mucocutaneous candidiasis, elevated serum IgE, and eosinophilia are the most common features of immunodeficiency and immune dysregulation in HIES patients. Some degree of eczema is seen in almost all HIES patients, although moderate-to-severe eczema is seen in only 71%, but may be as severe as documented in Fig. 1A. It usually manifests in the first few days or weeks of life, it is typically pruritic, and often lichenified (in a distribution not necessarily typical for AIDS because of the frequent involvement of the back, buttocks, and scalp). A newborn rash (Fig. 1B) is seen in 78% of HIES patients. Skin infections typically include staphylococcal furunculosis and cellulitis. The abscesses may occur anywhere but are most common around the face and trunk. The abscesses are well walled off in most

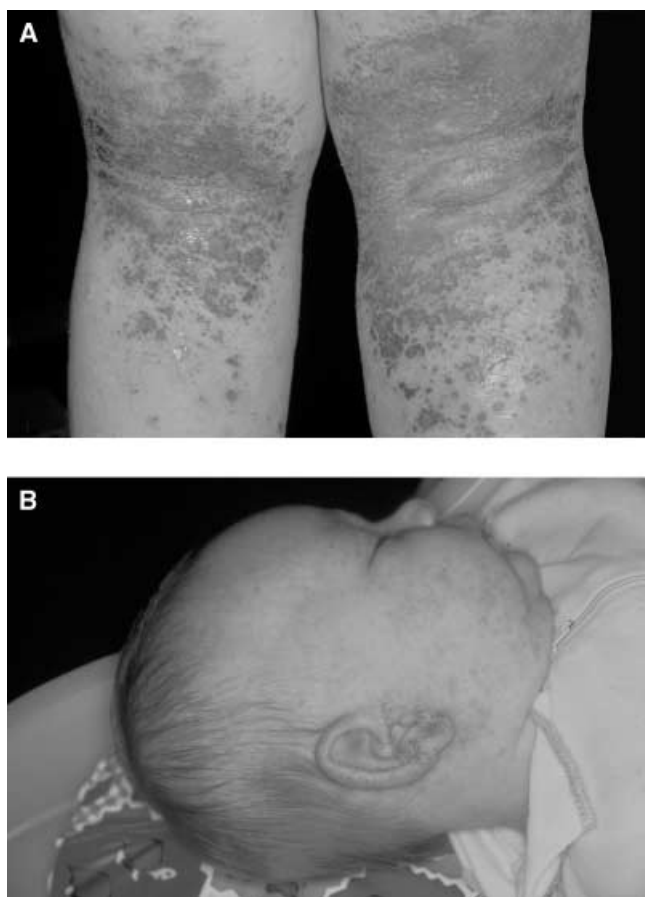


Figure 1. A. Impetiginized eczema in an 11-year-old girl with the hyper-IgE syndrome. The lesions responded well to systemic treatment with antistaphylococcal antibiotics and low-dose corticosteroids. B. 6-week-old infant with the autosomal dominant form of the hyper-IgE syndrome. Erythematous papular skin lesions appeared 4 weeks after birth and developed into eczema by age 6 weeks.

cases, filled with pus, and almost always grow *S. aureus*. Surgery to treat these lesions is common and they typically resolve without spreading through the dermis and fascia. Although “cold” abscesses have been said to be pathognomonic of HIES, they are not essential to the diagnosis. Following use of almost any prophylactic antibiotics, recurrent cutaneous abscesses are rare. In some patients, abscesses may be frequent early in life, but recently we have mostly seen impetiginized eczema. In our cohort, 89% of HIES patients had recurrent skin abscesses, and 81% had more than four recurrences.

Upper-respiratory infections, including sinusitis, bronchitis, otitis media, otitis externa and mastoiditis, are frequent in HIES. Seventy-one percent of patients reported four or more episodes per year.

A clinical hallmark of HIES is recurrent pneumonia. Most patients (90%) had at least one episode of pneumonia in their lifetime, but 76% had three or more bouts. Frequent pathogens of acute pneumonia in HIES are

S. aureus and *Haemophilus influenzae*. For reasons that are still unclear, pneumonias in HIES are frequently complicated. About three-quarters (77%) of HIES patients develop long-term pulmonary complications, including bronchiectasis and pneumatoceles. The cycle of infection and lung destruction is further exacerbated by superinfection of the cavities and bronchiectatic lung with *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. Pulmonary infections seen less commonly in HIES include *Pneumocystis carinii*, *Mycobacterium intracellulare*, and *Nocardia*.

Chronic candidiasis of mucosal sites and the nail beds affect 75% of HIES patients, including children. Cryptococcal infections of the esophagus and colon have also been reported in HIES (46, 47).

Facial and skeletal abnormalities associated with HIES were recognized in the original reports by Davis et al. in 1966 (33) and Buckley et al. in 1972 (34). We noted hyperextensibility in 71% of patients, and the characteristic facies in 87% of all HIES patients seen at the National Institutes of Health (NIH). The facial features develop progressively and become almost universal by late adolescence. Eighty-eight percent have an increased interalar distance (nasal width) and 65% have a high arched palate. Craniosynostosis has been previously reported in HIES (49–51), and has been seen at the NIH in one patient.

Recurrent pathologic fractures are further evidence of the multisystemic nature of HIES, occurring in 61% of patients. Osteopenia may be common in HIES and may be cytokine- or immune-driven (52, 53). Scoliosis has been seen in 66% of patients, arising from diverse conditions, including discrepancies in leg length, after thoracotomy (e.g. removal of a lung cyst), anomaly of the vertebral body, and idiopathic disease.

Impaired deciduation of primary teeth in HIES patients was only recently recognized, but it appears to be found quite consistently. Reduced resorption of primary tooth roots may lead to prolonged retention of the primary teeth, which in turn prevents the appropriate eruption of the permanent successors (54). However, the mechanism underlying this developmental abnormality is unknown. In our cohort of HIES patients who were older than 6 years, 73% displayed delayed dental deciduation. Our current practice is to determine the developmental age of the secondary teeth by radiography. If the primary teeth are significantly delayed in deciduation, we recommend extraction of retained primary teeth, which is usually followed by normal eruption of the permanent teeth.

Several malignancies have been reported in HIES, suggesting that these patients may be at some increased risk (55–61). In our cohort, two patients developed non-Hodgkin's lymphoma, and one had Hodgkin's disease. One patient developed metastatic squamous cell carcinoma of the tongue. To date, only one of our patients has developed systemic lupus erythematosus (62–65), and

not one has had autoimmune vasculitis (66), dermatomyositis (67), or membranoproliferative glomerulonephritis (68) (each of which has been previously reported in HIES).

The underlying cause of HIES is still unknown. Many studies have focused on the immune aspects of the disease, such as detection of eosinophilia in blood, sputum, and abscesses (51, 69), defective granulocyte chemotaxis (34, 35, 40, 70), abnormal T lymphocyte subsets (51, 71), defective antibody production (72–75), and decreased production of, or responsiveness to, cytokines such as IL-4 and interferon-gamma (IFN- γ) (76–79). Complement levels were normal when studied. Elevated levels of urinary histamine have been reported in some patients, and correlate with the extent of the eczematoid dermatitis (80). Although impaired neutrophil chemotaxis has been documented in HIES patients, this defect is inconsistently present, even in the same patient at different times (37, 81).

White blood cell counts are typically in the normal range, but have been reported to range from 1700 to 60 000/ μ l (37, 72). Chronic leukopenia with borderline neutropenia has been observed in several patients (37).

Some HIES patients also showed a defect in mixed lymphocyte culture proliferation to intrafamilial but not unrelated mononuclear cells (82). There is no association of human leukocyte antigen (HLA) with HIES (37, 72). In summary, no specific immune defect has been found consistently in all patients.

The clinically validated multicomponent scoring system (45) has some benefits compared to the uncommon laboratory tests described above for the diagnosis of HIES, and it is preferred.

In HIES, IgE levels of more than 10 000 IU/ml are characteristic and levels of > 50 000 IU/ml have been reported (36, 72). However, serum IgE levels are not static. Substantial fluctuations in serum IgE concentrations have been noted over time without any obvious change in the clinical presentation. For HIES, an IgE level of 10 times the normal limit (for adults > 2000 IU/ml) has been suggested as a reasonable diagnostic level.

The tropism of the elevated IgE in HIES is still unclear. A high proportion of the IgE in HIES binds to *S. aureus* and *Candida albicans* (83). Similar binding activity was not seen in other patients infected frequently with *S. aureus*, indicating that this abnormality is host-driven, and not organism-driven. However, raised antistaphylococcal titers are also seen in patients with AIDS and are therefore not diagnostic of HIES (84, 85). HIES patients have normal levels of anti-*S. aureus* IgG and modestly elevated levels of anti-*S. aureus* IgM. Unexpectedly, antistaphylococcal IgA levels are low in HIES patients (74) and total salivary IgA is also reduced. Quinti et al. (86), reported high-molecular-weight immune complexes (> 900 000 Da) composed of IgG anti-IgE. Buckley and Becker (72), found low antibody titers to diphtheria and tetanus, where only one out of 11 patients responded to a

booster inoculation. However, cytokine and proliferative responses *in vitro* to the mitogens phytohemagglutinin (PHA), concanavalin A, and pokeweed mitogen (PWM) have been essentially normal. In contrast, responses to *Candida* and tetanus *in vitro* have been low or absent.

In addition to IgE elevation, eosinophilia is seen in virtually all patients with HIES. The eosinophilia is at least two standard deviations above normal, and is usually above 700 cells/ μ l. Surprisingly, there is no correlation between the level of eosinophilia and the elevation of IgE. Moreover, the level of serum IgE is not correlated with disease activity or severity (36).

The specific regulation of IgE production and metabolism in HIES is still unresolved. IgE is greatly elevated during most phases of an HIES patient's life (36, 37, 72). IgE elevation was noted in the cord blood of a child born to a mother with HIES who subsequently developed HIES herself (87). Since IgE does not cross the placenta, this must reflect endogenous fetal synthesis of IgE suggesting that IgE dysregulation may be primary. With increasing age, IgE levels may fall below 2000 IU/ml, close to, or into the normal range. In five of 30 patients reported in the NIH series, IgE fell significantly, and yet they retained their increased susceptibility to infection (36).

IgE production may be elevated in HIES due to an increased number of B cells making subnormal levels of IgE (88). The nature of the driving force behind this abnormality is still unclear, but it is not particularly responsive to cytokines *in vivo* (76). Buckley and Becker (72) showed that unstimulated B cells from HIES patients had maximal rates of IgE synthesis *in vitro* that could not be augmented by exposure to PWM. However, coculture with parental, partially HLA-matched lymphocytes greatly reduced the IgE synthesis by HIES B cells *in vitro*. The IgE suppressive properties were in the CD8⁺ subset. These data suggest that the abnormality of IgE in HIES lies in the regulation of IgE synthesis, not in the synthesis of IgE *per se*.

Dreskin et al. (75) showed that IgE catabolism was defective in HIES, which may contribute to the elevation as well.

IFN- γ specifically inhibits the IgE-enhancing activity of Th-cell-line supernatants (23) and inhibits the effect of IL-4 on cell proliferation and induction of DNA synthesis (89). In HIES patients, there appears to be a reduction in lymphocytes producing either IFN- γ or tumor necrosis factor- α (TNF- α) (90). However, synthesis of IL-2 and IL-4 appears to be normal. A correlation between elevated *in vitro* IgE synthesis and diminished IFN- γ production in T cells has been found in HIES patients (90). Vercelli et al. (77) did not find modulation of IgE synthesis by IFN- γ *in vitro*, but suggested that T cell-independent mechanisms of IgE regulation were possible. King et al. (76) examined the effects of IFN- γ on HIES peripheral blood mononuclear cell production of IgE *in vitro* and *in vivo*. They used subcutaneous IFN- γ to treat five patients with HIES for 2–6 weeks. IFN- γ

suppressed spontaneous IgE production *in vitro* and *in vivo* in most of their patients, as was seen when peripheral blood mononuclear cells were assayed for spontaneous IgE production before and after IFN- γ administration. However, serum IgE levels fell in only two of five patients treated (one received 0.05 mg/m², the other received 0.1 mg/m²). Serum IgE levels rebounded to their pretreatment levels in both patients; three patients experienced no decline in serum IgE. No patient had any clinical change from the brief course of IFN- γ administration. Garraud et al. (88) showed that although both IFN- γ and IL-12 reduced IgE synthesis, neither cytokine could shut it off totally in HIES cells *in vitro*. Blocking antibodies to IL-4 and IL-13 reduced IgE production, while neutralization of both IL-4 and IL-13 completely suppressed IgE production in HIES cells *in vitro*. Interestingly, addition of IL-8 or blockade of IL-6 and TNF- α completely inhibited IgE production in HIES cells *in vitro*. Borges et al. (91) described decreased IFN- γ production *in vitro* in HIES, especially when the patients' cells were activated with staphylococcal antigen. They postulated that there is a shift towards a Th2-type cytokine response, which may result in deficient IFN- γ production and promote IL-4, IL-5, IL-13 and ultimately IgE production. However, we have not seen decreased IFN- γ production *in vitro* in response to PHA, suggesting that if this abnormality exists it may be antigen-specific (Frucht and Holland, unpublished observations).

Despite the interesting *in vitro* abnormalities related to IgE, the complex multisystemic nature of this disease and its effects on skin, bone, teeth, lung, immunity, and infection susceptibility, suggest an aberrant regulation of some cell or molecule that is common to all of these tissues, such as the monocyte and its derivatives, or endothelial cells.

Wiskott–Aldrich syndrome

The Wiskott–Aldrich syndrome (WAS) (OMIM #301000) is an X-linked, recessive, primary immunodeficiency with an approximate incidence of 1 in 250 000 individuals in Europe (92). WAS is characterized by thrombocytopenia, bloody diarrhea, eczema, recurrent infections, and a high incidence of malignancy (93, 94). X-linked thrombocytopenia (XLT) is a milder form of the same condition with predominant platelet abnormalities but minimal immunological disturbance (95–97).

The most invariable abnormality in WAS and XLT is thrombocytopenia with small platelet volume. This thrombocytopathy is responsible for the typical bleeding complications, such as intracranial hemorrhage after vaginal delivery, and bloody diarrhea in the perinatal period. Complications of bleeding are a frequent cause of death in WAS (23%) (94).

Clinical manifestations of the immune disorder in WAS include IgE-mediated allergy with eczema, food and drug allergies, susceptibility to severe and recurrent infections,

autoimmune phenomena, and increased incidence of lymphoproliferative disease.

Eczema, either mild and localized, or severe and generalized, is a consistent early manifestation of classic WAS. It is mostly pruritic and indistinguishable from that of classic AIDS except for purpuric lesions often present at sites of excoriation (Fig. 2). In WAS, eczema develops in 81% of the patients (94), but is not always present at the time of diagnosis. However, patients with the XLT phenotype have either mild and transient eczema or none at all. Bacterial antigens may play an important role in the persistence of chronic eczema, since the eczema of WAS patients often responds dramatically to treatment with systemic antibiotics (98). Immediate skin tests with inhalant and food allergens frequently yield positive results (99). Skin patch tests for allergic contact dermatitis are abnormal in 90% of patients studied (94). The eczema tends to be worse in families with an atopic diathesis. Thus, the severity of eczema may be controlled by genes associated with atopy, or modified by nutritional factors and available medical care.

Infectious complications are the most frequent cause of death in WAS (44%) (94). Recurrent infections may be pyogenic, viral, or opportunistic. The immune dysregulation may also manifest as autoimmune disease, including hemolytic anaemia, vasculitis, inflammatory polyarthritis, and inflammatory bowel disease (94). Malignancies including lymphoma, malignant reticuloendotheliosis, and leukemia are responsible for another 26% of deaths (94).

In WAS, however, both cellular immunity (T lymphocytes) and humoral immunity (B lymphocytes) are

impaired. The cellular defect has been attributed in part to the progressive depletion of T cells observed in these patients over time. During infancy, the number of circulating lymphocytes is normal. However, by 6–7 years of age, lymphopenia due to a net loss of T lymphocytes is common. This may be as a direct result of accelerated apoptosis, which was found in patients with classic WAS in the thymus and T-dependent pericortical areas of lymph nodes. In contrast, patients with XLT, who do not exhibit the profound immunodeficiency, did not exhibit increased apoptosis (100). Moreover, abnormal T cell function is suggested by diminished lymphocyte responses to mitogens, and depressed proliferative responses to allogenic cells and immobilized anti-CD3 monoclonal antibody (94, 101–103).

The humoral defect is demonstrated by low isohemagglutinin titers and consistently depressed antibody responses to polysaccharide and protein antigens (94,101,102,104). Moreover, following immunization B cells fail to develop immunologic memory, amplification, and class switching (94,102). Absolute B cell numbers usually remain within the normal range. Impairment of immunoglobulin levels is frequently observed in WAS and typically consists of low levels of IgM, normal levels of IgG, and increased levels of IgA, IgD, and IgE (32,105,106). In fact, the regular association of increased serum IgE concentrations with a particular immunodeficiency disorder was first noted in WAS (105,106). IgE in serum was elevated in 23 of 31 patients with Wiskott–Aldrich syndrome. However, only two of them had allergic asthma (107).

In one patient, bone-marrow transplantation resulted in partial chimerism due to engraftment of only donor T lymphocytes. This partial chimerism corrected the immune defect, including antibody response to polysaccharides, suggesting that the abnormal antibody production in WAS is largely caused by defective T lymphocyte function (108).

The gene causing WAS resides on the short arm of the X chromosome at Xp11.22–p11.23. It spans 9 Kb of genomic DNA, and is comprised of 12 exons. The 1823 base-pair cDNA encodes a 502 amino acid cytoplasmic protein called WAS-protein (WASP). Sequence analysis of the WAS gene has identified mutations of the same gene in both WAS and XLT (97,109). A large genotype–phenotype study of 48 unrelated families with WAS or XLT, undertaken by Zhu et al. (110), showed that missense mutations located in the first three exons generally resulted in a mild disease phenotype.

The proline-rich protein WASP is localized predominantly in the cytoplasm, with the highest protein density along the cell membrane. WASP belongs to a recently defined family of widely expressed proteins involved in the transduction of signals from membrane receptors to the actin cytoskeleton. It appears to be of central importance for the function of hematopoietic cells as it



Figure 2. Petechiae and hemorrhages together with eczema in an infant boy with Wiskott–Aldrich syndrome.

is constitutively expressed in all hemopoietic stem-cell-derived lineages (110).

But how may a protein involved in actin reorganization be responsible for the regulation of IgE? In WAS, T lymphocytes fail to proliferate upon stimulation through the antigen receptor, although they proliferate normally in response to mitogenic stimuli that bypass the antigen receptor. When stimulated with anti-CD3, normal T cells aggregate the T cell receptor. This receptor aggregation fails to occur in T cells of WASP knockout mice, since this process requires actin reorganization (111).

Moreover, WASP plays an important role in intracellular signaling of lymphocytes by interacting with the SH3 domains of selected cytoplasmic molecules. These molecules link intracellular signaling pathways to cell-surface receptors, such as B cell receptor (BCR) in B cells, and collagen receptors in platelets. These signaling pathways involve phosphorylation of WASP. In addition, WASP has been shown *in vivo* to bind the B cell Tec-family tyrosine kinase Btk. The genetic loss of Btk is known to be responsible for the X-linked form of agammaglobulinemia (112, 113).

Furthermore, WASP function is critically implicated in the collaboration of T and B lymphocytes. WAS T lymphocytes appear to be constitutively activated. In particular, WAS T cells display increased amounts of CD45RO, CD28, CD49, and other activation molecules (114).

For the above reasons, it seems possible that a defect in WAS may be directly involved in skewed immunoglobulin production and eczema.

Omenn syndrome

Omenn Syndrome (OS) (OMIM #267700) is a rare, autosomal recessive, severe combined primary immunodeficiency characterized by lymphadenopathy, hepatosplenomegaly, and early onset generalized erythroderma (115–117) (Fig. 3). In addition, patients with OS have protracted diarrhea and failure to thrive. Unless treated by bone-marrow transplantation, OS patients typically die of overwhelming infections and severe metabolic disturbances within the first months of life (118). Main laboratory findings in OS are eosinophilia with increased serum IgE in the setting of hypogammaglobulinemia of IgG, IgA, and IgM.

Omenn syndrome is caused by mutations in either one of the human recombination activating genes 1 or 2 (*RAG1*, *RAG2*) that impair, but do not abolish, recombination activity (119). Null mutations (those that completely eliminate the recombination activity of RAG proteins) cause a complete block of T cell and B cell development and lead to severe combined immune deficiency (SCID) with absence of mature T and B lymphocytes (T⁺B⁺ SCID) (120). However, the *RAG* gene mutations identified in OS patients allow rearrangement



Figure 3. Omenn syndrome with alopecia, acute generalized dermatitis, pruritus, enlarged lymph nodes, and hepatosplenomegaly in a 6-month-old boy.

of T-cell receptor (TCR) gene segments, albeit with reduced efficiency. Therefore, abnormalities in RAG proteins can give rise to either T⁺B⁺ SCID or OS, depending on the severity of the mutation (121). In a cohort of nine patients with T⁺B⁺ SCID due to *RAG* mutations, six had mutations in the *RAG1* gene, and three in *RAG2*; in a series of 18 patients with Omenn syndrome,

14 had mutations in *RAG1*, and four in *RAG2*, respectively (121).

Pre-B cells and pre-T cells do not survive during lymphocyte development if they do not receive survival signals from the pre-B- and pre-T-cell receptors, respectively. The heavy chain of the IgM molecule and the TCR β -chain are necessary constituents of their respective receptors. In the case of complete RAG deficiency, V(D)J recombination cannot be initiated: IgM and TCR β -chains are not synthesized and are not available for the pre-B- or pre-T-cell receptors. Thus, the precursor lymphocyte receives no survival signal and dies. This explains the alymphocytosis in patients with complete RAG1 and RAG2 deficiencies (T⁺B⁺ SCID) (122).

In contrast to T⁺B⁺ SCID, in which eosinophilia and elevated IgE are absent, the defect in OS permits the occurrence of some rearrangements. For this reason, some T cells with *bona fide* TCR rearrangements can exit the thymus, or expand either in the thymus itself, or in the periphery, and produce Th2-type cytokines (122). These in turn may be responsible for some features of the characteristic phenotype of OS, such as hypereosinophilia and increased IgE. Upon activation *in vitro* T cells of OS patients predominantly secrete Th2-type cytokines IL-4, IL-5, IL-10 (123–125). Accordingly, serum levels of IL-4 and IL-5 are increased, and the synthesis of IL-2 and IFN- γ is reduced. Therefore, skewing toward Th2 appears to be the result of the underlying defect in the RAG genes, in part accounting for the OS phenotype.

Although complete RAG-deficient patients had very low numbers of CD19⁺ B cells, residual B cells (more than 3%) were found in three of 16 patients with OS (121). The serum levels of IgG, IgA, and IgM are markedly reduced, and antibody production *in vivo* is severely impaired, but not completely abolished (116). This is also indicated by the low but measurable IgM-restricted antibody response to immunization with bacteriophage ϕ X174 (117). In addition, hypogammaglobulinemia may be partially due to enteral protein loss (122).

There has been a great interest in the possible role of IgE in the profound infection-susceptibility of infants with OS. Despite lymphopenia and reduced levels of IgG, IgA, and IgM, affected infants have a persistent leukocytosis with marked eosinophilia, and elevated serum IgE levels. In a recent report by Villa et al. (2001) 41 patients with RAG mutations were analyzed. Of 41 patients, 17 had OS, 11 had atypical OS/SCID, and 16 had T⁺B⁺ SCID. An IgE level was determined in 27/41 and was > 200 IU/l in 11 (121). Seven of the 11 patients had OS, while the remaining four patients had atypical SCID/OS; none of the patients with T⁺B⁺ SCID tested, had elevated IgE levels. Thus, an elevated IgE level only occurred in OS or SCID/OS variant phenotypes and was restricted to missense mutations in the *RAG* gene, whereas null mutations in *RAG* resulting in T⁺B⁺ SCID were not associated with an elevated serum IgE (121). Cutaneous manifestations were documented in 31 out of

41 patients with *RAG* mutations. Importantly, generalized erythroderma was documented in 15 of the 17 patients with OS, but only in two of the 16 patients with T⁺B⁺ SCID (121).

Further research in OS may answer the question why partial V(D)J recombination activity leads to elevated IgE levels. Moreover, as B lymphocytes are usually undetectable in the lymph nodes and in the gut, it remains unknown where IgE secretion in OS occurs.

The Comèl–Netherton syndrome

The Comèl–Netherton syndrome (NS) (OMIM #256500) is a rare but severe autosomal recessive, multisystemic disorder. NS was first reported by Comèl in 1949 and Netherton in 1958 (126,127). NS is characterized by localized or generalized congenital ichthyosis with defective cornification, specific hair-shaft abnormalities (trichorrhexis invaginata or “bamboo hair”), immune deficiency, hypereosinophilia, and markedly elevated IgE levels, the latter most likely responsible for severe IgE-mediated manifestations including AEDS and allergic rhinitis (128, 129).

NS presents at or soon after birth with generalized erythroderma covered by fine, translucent scales, which can be difficult to distinguish clinically from erythrodermic psoriasis, nonbullous congenital ichthyosiform erythroderma, or other infantile erythrodermas (Fig. 4). Whereas in individuals with severe disease the generalized ichthyosiform erythroderma persists throughout life, the ichthyosis in most patients gradually evolves into migratory, serpiginous, scaling, and erythematous plaques, which are bordered by a peculiar double-edged scale that is descriptively named ichthyosis linearis circumflexa. The skin lesions are often pruritic, resemble AEDS, and show an unstable, undulating course. Characteristically, they do not respond to topical corticosteroids (129).

The hallmark of NS is the so-called “bamboo hair” and other hair-shaft abnormalities including pili torti (twisted hair) and trichorrhexis nodosa (hair of varying diameter). These hair-shaft abnormalities develop during early childhood and may result in diffuse alopecia (127, 129–131).

In about 20% of patients the neonatal period is complicated by failure to thrive, recurrent infections, and enteropathy leading to hypernatremic dehydration and electrolyte imbalances. These complications can be fatal and may, at least in part, be attributed to impaired permeability of the epidermal barrier, which may be caused by premature secretion of so-called “lamellar-body contents” seen in NS (132).

In NS, IgG levels are characteristically low and may contribute to the increased susceptibility to skin, respiratory tract, and systemic infections. In contrast, IgE levels are markedly elevated. This may contribute to the characteristic allergic manifestations such as reactions to food and common allergens. The pathogenesis of IgE



Figure 4. Infant with Comèl–Netherton syndrome. The generalized erythroderma covered by fine, translucent scales persisted through the first year of life. Picture kindly provided by F. Kaut, Dermatology Department, University of Freiburg, Germany.

elevations in NS is of considerable interest because of the peculiar association of skin, hair, and immunologic abnormalities in the context of a monogenic disorder. In 20 patients with NS, the IgE level was found to be between 100 and 1000 IU/ml in four patients, > 1000 up to 10 000 IU/ml in 12 patients, and > 10 000 IU/ml in four patients, respectively (133). Interestingly, the extent of IgE elevation did not correlate with the presence of severe infections.

Most cases of NS are sporadic; however, there are reports of affected sibships and of consanguinity in about 10% of the families with NS, consistent with autosomal recessive inheritance (134). Using these sibships in a genome-wide linkage-screen, NS was mapped to a 4 cM interval on chromosome 5q32 (135). Evaluation of candidate genes within this region revealed that NS is caused by mutations in the serine protease inhibitor gene *SPINK5* (136). This 61 Kb gene consists of 33 exons and encodes a recently discovered Kazal-type serine protease

inhibitor (designated LEKTI). *SPINK5* (LEKTI) is the first serine-protease inhibitor shown to be responsible for skin disease, hair morphogenesis, immunodeficiency, and IgE elevation. Genotype–phenotype correlations suggest that homozygous nucleotide changes resulting in premature truncation of *SPINK5* (LEKTI) are associated with a severe phenotype (133).

Protease inhibitors play a central role in the maintenance of many physiological functions such as food digestion, blood coagulation, and remodeling of extracellular matrix, by limiting unwanted proteolytic activities and thereby regulating cell migration, proliferation, and differentiation. Although pancreatic secretory trypsin inhibitor is a prototype of Kazal-type serine protease inhibitors (137), the physiologic substrates of *SPINK5* are currently unknown. Therefore, the pathophysiologic mechanism leading to this complex disease remains to be elucidated. A wide variety of protease inhibitors, including LEKTI are expressed in the skin, suggesting that these enzymes may be involved in controlling epidermal cell growth and differentiation, and suggesting a possible mechanism for the epidermal dysfunction observed in NS. Diminution or loss of the granular and horny layers has been described in NS patients, suggesting that *SPINK5* mutations cause a distinctive defect in function of the skin barrier in NS. Defective cornification may favor recurrent infections and inflammation in NS.

Since *SPINK5* is highly expressed in the thymus (138), defective LEKTI expression may be expected to have a deleterious effect on T cell differentiation. Abnormal maturation of T lymphocytes in NS may disrupt the regulation of Th2 responsiveness to allergens, thereby driving the acute hypersensitivity response and IgE levels. This finding suggests the existence of a novel pathway distinct from interleukin signaling and V(D)J recombination involved in the regulation of T lymphocyte development.

It is also possible that, like other serine protease inhibitors, LEKTI is expressed as part of a cytokine activated acute-phase response (136, 139). Thus, defective LEKTI expression may impair the organism's response to external assault. Moreover, proteolysis is critical in cell activation and communication, and some inhibitors of serine protease have been shown to down-regulate the proinflammatory nuclear factor (NF)- κ B pathway, providing a possible link between LEKTI and the immune dysregulation seen in NS. Targeting of *SPINK5* should unravel new molecular bases of immunity and IgE-mediated disorders, such as atopy.

Concluding remarks

Elevation of IgE is associated with several primary immunodeficiency disorders (PID) such as the hyper-IgE syndrome (HIES), Wiskott–Aldrich syndrome (WAS), Omenn syndrome (OS), Comèl–Netherton syndrome (NS), thymic hypoplasia syndromes, and others.

In the 1970s and 1980s case and small cohort reports of patients with PID added to the knowledge of the incidence and extent of IgE elevation in PID. In the 1990s, molecular genetic approaches revealed some causes of PIDs with elevated IgE, such as the WASP defect in WAS, the *RAG* mutations in OS, and the *SPINK5* mutations in NS. However, because of the apparent and unexpected complexity of the proteins responsible for PID and IgE dysregulation, these findings have so far added only little to the understanding of the pathophysiologic mechanisms of IgE production. Accumulating further knowledge about the role of IgE in PID may prove helpful in understanding common but complex diseases such as IgE-mediated allergic hypersensitivity.

Further research focusing on the mechanisms of these genetic defects in IgE regulation is needed if we are to move from a phenomenological to a rational basis for both the understanding of these diseases as well as the application of these understandings to therapeutics.

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