

Hyper-IgE Syndromes

Haitham M. Saleh; Nishad C. Sathe.

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Continuing Education Activity

Hyperimmunoglobulin E syndromes are rare immunologic disorders characterized by recurrent cutaneous and sinopulmonary infections, infantile dermatitis, markedly elevated immunoglobulin E levels, and variable skeletal, dental, vascular, neurologic, and malignant complications. Delayed recognition, incomplete genetic evaluation, and inconsistent coordination of infectious, immunologic, orthopedic, dental, and cardiovascular care can increase morbidity and mortality. This continuing medical education activity addresses the clinical distinction between signal transducer and activator of transcription 3 gene–associated disease, dedicator of cytokinesis 8 gene deficiency, and other overlapping genetic variants. Participants will review diagnostic criteria, genetic testing strategies, laboratory and imaging findings, differential diagnosis, infection prevention, antimicrobial therapy, biologic treatment, transplant considerations, and complication monitoring. The activity is designed to strengthen diagnostic accuracy, support evidence-based treatment selection, improve risk assessment, reduce preventable complications, and promote coordinated interprofessional care for patients with hyperimmunoglobulin E syndromes.

Objectives:

- Differentiate hyperimmunoglobulin E syndromes from atopic dermatitis, Wiskott-Aldrich syndrome, Netherton syndrome, Omenn syndrome, DiGeorge syndrome, and other disorders with elevated immunoglobulin E levels or eczematous dermatitis.
- Identify clinical features that distinguish signal transducer and activator of transcription 3 gene–associated hyperimmunoglobulin E syndrome from dedicator of cytokinesis 8 gene deficiency and other overlapping immunodeficiency disorders.
- Select evidence-based treatment strategies for infectious and inflammatory manifestations, including abscess drainage, antimicrobial therapy, immunoglobulin therapy, biologic therapy, and transplant referral when appropriate.
- Coordinate interprofessional care among immunology, infectious disease, hematology, primary care, nursing, pharmacy, orthopedics, dentistry, and cardiovascular specialists to improve patient-centered outcomes.

Introduction

Hyperimmunoglobulin E syndromes (HIESs) are defined by the triad of recurrent cutaneous and sinopulmonary infections, dermatitis beginning in infancy or early childhood, and markedly elevated immunoglobulin E (IgE) levels. David et al first described autosomal dominant HIES as Job syndrome in 1966 in 2 patients with eczema, recurrent pulmonary infections, and cold lung abscesses (see **Image**. Job Syndrome). Later, in 1972, Buckley et al reported an association between this condition and elevated serum IgE levels and a series of phenotypic features. In 2007, researchers discovered that classic autosomal dominant HIES is caused by deficiency of the signal transducer and activator of transcription 3 (*STAT3*) gene. Subsequently, numerous other HIES variants resulting from abnormalities in proteins involved in *STAT3* signaling or other immune regulatory pathways have been recognized.[\[1\]\[2\]\[3\]](#)

Etiology

The hyper-IgE syndromes are classified into 2 types:

- **Type I:** Autosomal dominant hyper-IgE syndrome (AD-HIES), also known as Job syndrome or signal transducer and activator of transcription 3 (*STAT3*) gene–HIES, in which patients generally exhibit several nonimmunologic features, including connective tissue, dental, and skeletal abnormalities.
- **Type II:** Autosomal recessive hyperimmunoglobulin E syndrome (AR-HIES), also known as dedicator of cytokinesis 8 (*DOCK8*) gene–HIES, which has a higher incidence of neurologic complications and cutaneous viral infections.

Newer classifications include phosphoglucomutase 3 gene (*PGM3*), tyrosine kinase 2 gene (*TYK2*), zinc finger protein 341 gene (*ZNF341*), caspase recruitment domain family member 11 gene (*CARD11*), and interleukin 6 receptor gene (*IL6R*) deficiencies, which can produce overlapping symptoms.[\[4\]](#)

Epidemiology

Autosomal dominant hyper-IgE syndrome is an uncommon condition, and its actual incidence remains undetermined. The incidence of this disease exists across all racial and ethnic groups, exhibiting no apparent sex predilection. The disease typically develops in infancy, but diagnosis may be delayed until childhood or adulthood. Enhanced awareness and genetic testing have facilitated the early identification of affected families. AR-HIES, predominantly resulting from *DOCK8* deficiency, is infrequent and manifests in both consanguineous and nonconsanguineous populations.

Pathophysiology

Heterozygous mutations in the signal transducer and activator of transcription 3 gene (*STAT3*) result in classic autosomal dominant hyperimmunoglobulin E syndrome (HIES), often known as *STAT3*-HIES. Various combinations of receptor-associated Janus kinases and STAT proteins transduce cytokine signals; following Janus kinase–mediated phosphorylation, the STAT proteins dimerize, translocate to

the nucleus, and activate target genes. Vulnerability to bacterial and candidal infections in HIES underscores the importance of STAT3-dependent cytokines (eg, interleukin [IL]-6, IL-21, and IL-23) in the differentiation of IL-17-producing CD4⁺ T cells that contribute to defense against these pathogens. Insufficient stimulation of β -defensin synthesis by IL-22, produced by T helper 17 cells and signaling through STAT3, may facilitate the onset of infections at epithelial surfaces (eg, skin and lungs) in *STAT3*-HIES. The STAT3 protein is essential for the signaling pathways of IL-6, which facilitates acute-phase responses and functions as a pyrogen, and of IL-10, an anti-inflammatory cytokine. STAT3 deficiency explains the occurrence of cold abscesses and the damaging inflammation, such as that found in the lung, which are characteristic of HIES. Impaired production of IL-10–induced tolerogenic dendritic cells and forkhead box P3–positive regulatory T cells may exacerbate other inflammatory characteristics of HIES, including atopic-like dermatitis and elevated IgE levels.^[5] STAT3 also inhibits osteoclast development, and osteoporosis is characteristic of STAT3 deficiency in both mice and patients with HIES. Finally, leukocytes from persons lacking STAT3 generate elevated levels of interferon- γ and tumor necrosis factor (TNF) when stimulated with IL-12 and lipopolysaccharide/interferon- γ , respectively, compared with leukocytes from unaffected controls.^{[1][2]}

Additional variants of hyperimmunoglobulin E syndrome may arise from the disruption of STAT3 signaling, including deficiencies in the following proteins: the IL-6 receptor (autosomal recessive) and IL-6 signal transducer (glycoprotein 130; autosomal dominant or autosomal recessive); phosphoglucomutase 3 (PGM3; autosomal recessive), which enhances glycoprotein 130 expression; zinc finger protein 341 (ZNF341; autosomal recessive), which modulates STAT3 expression; and ERBIN (autosomal dominant), whose expression is induced by STAT3. Generally, these conditions exhibit clinical characteristics that overlap with those of *STAT3*-HIES, including additional manifestations such as autoimmunity and cognitive impairment in PGM3 deficiency and craniosynostosis in autosomal recessive glycoprotein 130 deficiency.^[6]

DOCK8 deficiency is an autosomal recessive disorder that shares the characteristics of HIES. The *DOCK8* protein associates with the Wiskott-Aldrich syndrome protein in a complex that connects T-cell receptors to the actin cytoskeleton. *DOCK8* deficiency leads to increased T helper 2 cells and the synthesis of the pruritogen IL-31 while concurrently reducing T helper 1 and T helper 17 cells.^{[7][8][9]} The caspase recruitment domain family member 11 (*CARD11*) gene–associated atopy with dominant interference with nuclear factor κ B signaling arises from heterozygous dominant-negative mutations in *CARD11*, which encodes a scaffolding protein integral to lymphocyte receptor signaling. Patients exhibit the distinctive HIES triad along with additional atopic symptoms and B-cell lymphopenia. The characteristics of HIES have also been recognized in a subset of individuals with homozygous mutations in the tyrosine kinase 2 gene (*TYK2*), a member of the Janus kinase family. Affected patients exhibit deficiencies in the signaling pathways for IL-12 and interferon- α/β , resulting in increased vulnerability to mycobacterial and viral infections and alterations in IL-6 and IL-10 levels.^{[10][11]}

Histopathology

The papulopustular eruption in *STAT3*-HIES is histologically defined by eosinophilic folliculitis, eosinophilic spongiosis, and a superficial and deep perivascular infiltration rich in eosinophils.^{[12][13]}

History and Physical

The classic autosomal dominant form (*STAT3*-HIES) is characterized by clinical signs of immunological and nonimmunological features:

Immunological Features

Individuals with *STAT3*-HIES generally present within the first month of life with a noninfectious folliculocentric papulopustular eruption affecting the face, scalp, neck, axillae, and diaper region (see **Image**. Job syndrome). Chronic candidiasis of the oral mucosa, periungual regions, and nails affects approximately 80% of patients with HIES and may signify the initial infectious presentation in infancy.^[13] Cutaneous staphylococcal infections involve impetiginized plaques, retroauricular fissures, folliculitis, furunculosis, abscesses, cellulitis, lymphangitis, and paronychia, which can result in nail dystrophy. Cutaneous abscesses are frequently large and predominantly affect the neck, scalp, periorbital region, axillae, and groin. These lesions are called cold abscesses because they lack the redness and tenderness typically observed in healthy individuals. Patients frequently are afebrile or exhibit only a low-grade fever. Although the abscesses are predominantly staphylococcal, many patients also experience recurrent skin infections caused by other pathogens, including *Streptococcus pyogenes* and *Candida albicans*.^[13] The eczematous rash associated with HIES has numerous clinical features similar to those of atopic dermatitis, such as intense itching, lichenification, and staphylococcal superinfection. This rash is typically observed in young children but often resolves by puberty. In contrast to patients with atopic dermatitis, patients with *STAT3*-HIES typically do not display allergic rhinitis, **asthma**, or other dermatological manifestations of atopy.^[13]

Although many patients with *STAT3*-HIES exhibit only cutaneous signs, most also experience recurrent bronchitis and pneumonia. *Staphylococcus aureus* and *Haemophilus influenzae* organisms typically cause lung infections that can lead to empyema, bronchiectasis, and pneumatocele formation. Pneumatocelles often persist and become susceptible to recurrent infections by bacterial or fungal agents, especially *Aspergillus* species. Occasionally, significant hemoptysis occurs. *Pneumocystis jirovecii* pneumonia may also manifest in newborns and children with *STAT3*-HIES. Additional common locations of infection include the ears, oral mucosa, sinuses, and eyes. Visceral infections, except pneumonia, are uncommon. However, deep-seated infection has been reported as a retroperitoneal abscess.^[14]

Nonimmunological Features

Patients with *STAT3*-HIES exhibit gradual facial coarsening characterized by thickened, doughy skin, enlarged follicular ostia, pitted scarring, a broad nasal bridge, a wide, fleshy nasal tip, deep-set eyes, a prominent forehead, and irregularly proportioned cheeks and jaw. Osteopenia is frequently observed and is associated with an increased risk of fractures in the long bones, ribs, and pelvis. More than 50% of adolescents and adults with *STAT3*-HIES have experienced at least 3 fractures, sometimes resulting from undiagnosed or minor trauma. Scoliosis is present in 75% of patients aged 16 years or older, whereas joint hyperextensibility affects approximately 70% of patients. About 50% of patients with *STAT3*-HIES exhibit a high-arched palate, and distinctive dental manifestations include retention of primary teeth due to inadequate root resorption and absence of eruption of secondary teeth.

Numerous cerebral anomalies have been identified, including Chiari malformations, lacunar infarctions, and localized white matter hyperintensities on T2-weighted magnetic resonance imaging.

The occurrence of coronary artery aneurysms in adults has also been documented. HIES is associated with an increased risk of B-cell-origin non-Hodgkin lymphoma.

DOCK8 deficiency resembles *STAT3*-HIES, characterized by markedly elevated serum IgE levels, peripheral eosinophilia, chronic eczematous dermatitis, recurrent staphylococcal skin infections (including cold abscesses), respiratory tract infections, and mucocutaneous candidiasis. However, skeletal and dental deformities, facial coarsening, and pneumatocoeles are not defining characteristics. Individuals with *DOCK8* deficiency are susceptible to warts, molluscum contagiosum, severe herpes simplex, and varicella-zoster virus infections, as well as opportunistic infections. Further manifestations include **asthma**, food allergies leading to anaphylaxis, autoimmunity, cerebral vasculitis, mucocutaneous squamous cell carcinomas, and lymphomas. Up to 50% of patients die by age 20 years due to infection, malignant neoplasms, or central nervous system disorders.[\[15\]](#)[\[16\]](#)

Evaluation

Genetic testing is the optimal diagnostic approach. *STAT3* sequencing confirms the presence of autosomal dominant hyper-IgE syndrome. Testing for *DOCK8* deficiency should be conducted when severe viral infections, food allergies, or failure to thrive are significant characteristics. Additional uncommon etiologies include mutations of *TYK2* and *ZNF341*.[\[17\]](#) Patients with HIES exhibit very high blood concentrations of polyclonal IgE, typically exceeding 2000 IU/mL, which occasionally diminish in adulthood. Patients have elevated concentrations of antistaphylococcal and anticandidal IgE antibodies and frequently experience acute wheal-and-flare responses to various dietary and environmental allergens. Numerous affected patients exhibit eosinophilia in both peripheral blood and sputum. Cell-mediated immunity is frequently abnormal, evidenced by anergy in skin testing and diminished in vitro lymphoproliferative responses to certain antigens. Serum concentrations of IgG, IgA, and IgM are often within reference ranges in *STAT3*-HIES, as are lymphocyte subsets. Chest radiography, chest CT, or both are essential for assessing the extent of lung parenchymal involvement in autosomal dominant HIES.[\[18\]](#) Conversely, *DOCK8* deficiency represents a mixed immunodeficiency marked by lymphopenia, defined by a deficit of CD4+ T cells relative to CD8+ T cells and B cells, diminished IgM levels, fluctuating IgG levels, raised IgE levels, and peripheral eosinophilia.[\[19\]](#)[\[20\]](#)

Treatment / Management

The management of infectious challenges in HIES involves incision and drainage of abscesses, along with both therapeutic and preventive antibiotic therapy. Interferon- γ has demonstrated efficacy in managing infections, while intravenous immunoglobulin may improve dermatitis, prevent infections, and reduce IgE levels. The administration of dupilumab and omalizumab has been shown to improve eczematous dermatitis associated with HIES.[\[21\]](#)[\[22\]](#)

The treatment of nonimmunologic manifestations must be managed by an interprofessional team to prevent complications. Consequently, scoliosis, depending on its severity, as well as bone fractures and degenerative joint disease, may require orthopedic surgical procedures. Dental abnormalities

require adequate stomatologic treatment. Cardiovascular complications are treated in a specialized environment.[\[23\]](#)[\[24\]](#)[\[25\]](#)[\[26\]](#)

Bone-marrow transplant has yielded variable outcomes in these patients.[\[27\]](#) Hematopoietic stem cell transplantation is typically recommended for severe *DOCK8*-related disorders or refractory *STAT3*-HIES when standard treatments are inadequate. In *DOCK8*-HIES, hematopoietic stem cell transplant is considered curative when performed before irreversible end-organ damage, restoring T-cell and natural killer cell function and significantly reducing the infection burden.[\[28\]](#)[\[29\]](#)

Differential Diagnosis

The current diagnostic criteria for *STAT3*-HIES require an IgE level exceeding 1000 IU/mL and a cumulative score of 5 clinical symptoms, which include pneumonia (confirmed by radiography), newborn papulopustular eruption (occurring during the first 3 weeks of life), pathologic bone fractures, distinctive facial features, and a high-arched palate. The presence of these traits, along with a deficiency of T helper 17 cells or a heterozygous *STAT3* mutation, supports a probable or definitive diagnosis, respectively.[\[30\]](#)

Hyper-IgE syndromes must be distinguished from several other disorders that may present with elevated IgE levels and a skin eruption, including atopic dermatitis, Wiskott-Aldrich syndrome, Netherton syndrome, Omenn syndrome, DiGeorge syndrome, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, *ARPC1B* (actin-related protein 2 and 3 complex subunit 1B) gene deficiency, Loeys-Dietz syndrome, and graft-versus-host disease. Atopic dermatitis and Wiskott-Aldrich disease are sometimes confused with HIES because of their eczematous dermatitis and staphylococcal infections. Nonetheless, the emergence of cold abscesses, recurrent pneumonia, pronounced facial features, and osteopenia helps distinguish *STAT3*-HIES from these conditions, whereas platelet anomalies help distinguish Wiskott-Aldrich syndrome and *ARPC1B* syndrome. Moreover, the rash typically manifests at birth or within the first few weeks, in contrast to atopic dermatitis, which typically emerges after age 3 months. Flow cytometry would also reveal a notable decrease in T helper 17 cells in *STAT3*-HIES and an excess of T helper 2 cells in atopic dermatitis.

Patients with prolidase deficiency exhibit elevated IgE levels, susceptibility to pyogenic infections, and eczematous dermatitis, alongside recurrent leg ulcers, facial dysmorphism, and intellectual disability. Patients with chronic granulomatous disease and myeloperoxidase deficiency develop bacterial and candidal abscesses; nevertheless, they generally do not have significantly elevated IgE levels. CD4⁺ lymphocytopenia may be a prominent feature of *DOCK8* deficiency and other immunodeficiency disorders associated with a predisposition to verruca formation, including epidermodysplasia verruciformis and Netherton syndrome.

Prognosis

Patients with AD-HIES experience a shortened lifespan, with mortality primarily occurring in adulthood due to chronic lung infections. Historically, within a specific cohort, the mean age of surviving patients was 27 years, while infection-related mortality occurred, on average, at 29 years.[\[31\]](#) Mortality is typically associated with complications from pneumatoceles or bronchiectasis,

including secondary infections by molds such as *Aspergillus* or *Scedosporium* species, which can result in vascular invasion, metastatic dissemination, or fatal hemoptysis. Patients also face an elevated risk for hematologic malignancies, such as Hodgkin and non-Hodgkin lymphoma.^[32] Although autosomal dominant-HIES is associated with high morbidity and mortality, advances in medical care and close monitoring have led to a recent improvement in prognosis.^{[23][33]} Conversely, autosomal recessive hyper-IgE syndrome resulting from *DOCK8* deficiency is linked to markedly increased mortality in the absence of hematopoietic stem cell transplant. Autosomal recessive HIES is also associated with more deaths due to sepsis, central nervous system infections, and vasculitis than autosomal dominant HIES.^[34]

Complications

Complications stem from recurrent infections, anatomic anomalies, and immunologic dysregulation, and pulmonary disease is the primary cause of morbidity and mortality. Other complications include:

- Malignant neoplasms, especially non-Hodgkin lymphoma. Other cancers have also been reported, such as Hodgkin lymphoma and cancers of the vulva and lung
- Autoimmune diseases like systemic lupus erythematosus, membranoproliferative glomerulonephritis, vasculitis, and dermatomyositis
- Hypertension associated with vascular abnormalities
- Myocardial infarction due to the rupture of coronary aneurysms
- Lacunar infarcts due to the rupture of cerebral aneurysms ^{[27][35]}

Deterrence and Patient Education

Patients should maintain follow-up with an immunologist and an interprofessional care team because the disorder affects multiple organ systems. Maintaining general hygiene is vital for reducing the risk of infection.

Pearls and Other Issues

Dominant-negative mutations in the *STAT3* gene are the primary etiologic cause of HIES. The autosomal recessive form of HIES is caused by loss-of-function mutations in the *DOCK8* gene. *STAT3* binds to the promoters of genes, including those involved in cytokine signaling, leukemia inhibitory factor, corticotropin, oncostatin, receptor tyrosine kinases, insulin-like growth factor 1, and growth hormone. Therefore, *STAT3* is critical for cell survival and inflammation in the skin, lungs, thymus, mammary glands, macrophages, neurons, and lymphocytes. Mutations affecting hepatic IL-6 responses alter acute-phase protein synthesis.^[36] The condition is characterized by defects in immunity with eczematous and nonimmunologic systemic disorders. Antenatal diagnosis is theoretically possible. However, the very low incidence and sporadic nature in most cases make this method of little interest. Current treatment is purely symptomatic. Early detection and treatment of infections are essential for disease treatment. Exposure to chlorinated water or dilute bleach baths

can diminish staphylococcal skin colonization. Bacillus Calmette-Guérin vaccination is contraindicated in patients with known or suspected immunologic deficits, and live vaccines should be deferred until age 6 months.[\[37\]](#) Immunology research has led to the discovery of new treatment options and improved understanding of HIES. The addition of omalizumab to standard treatment may improve pulmonary and dermatologic symptoms.[\[38\]](#) Further research is needed to improve HIES diagnosis and care, as substantial gaps remain in our understanding of the disorder.[\[39\]](#)

Enhancing Healthcare Team Outcomes

The hyper-IgE syndromes are rare immunologic disorders characterized by recurrent infections. Early identification and treatment of patients with these syndromes are imperative for reducing morbidity and mortality. The care of patients with these conditions requires collaboration among healthcare professionals to ensure patient-centered care and improve overall outcomes. The conditions are primarily treated by hematologists and infectious disease specialists, whereas outpatient follow-up is conducted by primary care clinicians and nurse practitioners as part of interprofessional team care. Most of these patients require long-term antibiotic therapy combined with abscess drainage, so pharmacist consultation is necessary to appropriately target antimicrobial therapy. The treatment of nonimmunologic manifestations must be interprofessional to treat and prevent complications. Consequently, scoliosis, depending on its severity, as well as bone fractures and degenerative joint disease, may require orthopedic surgical procedures. Dental abnormalities require adequate stomatologic treatment. Cardiovascular complications are treated in a specialized environment. An outpatient nurse should make regular home visits to ensure the patient's health remains stable and report findings to the healthcare team.

A strategic approach is equally crucial and should include evidence-based strategies to optimize treatment plans and minimize adverse effects. Ethical considerations must guide decision-making to ensure informed consent and respect patient autonomy in treatment choices. Each healthcare professional must be aware of their responsibilities and contribute specific expertise to the patient's care plan, fostering an interprofessional approach. Effective interprofessional communication is paramount, allowing seamless information exchange and collaborative decision-making among team members. Care coordination plays a pivotal role in ensuring that the patient's journey from diagnosis to treatment and follow-up is well coordinated, minimizing errors and enhancing patient safety. By embracing these principles of skill, strategy, ethics, responsibilities, interprofessional communication, and care coordination, healthcare professionals can deliver patient-centered care, ultimately improving patient outcomes and enhancing team performance in the treatment of hyper-IgE syndromes.

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