The Hyper-IgE Syndromes: Lessons in Nature, From Bench to Bedside

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Abstract: Hyper-IgE syndrome is a primary immunodeficiency marked by abnormalities in the coordination of cell–cell signaling with the potential to affect T_H17 cell, B cell, and neutrophil responses. Clinical manifestations include recurrent skin and lung infections, serum IgE elevation, connective tissue repair and development alterations, and the propensity for vascular abnormalities and tumor development. Signal transducer and activator of transcription 3 (STAT3) signaling, dedicator of cytokinesis 8 (DOCK8) signaling, and tyrosine kinase 2 (TYK2) signaling alterations have been implicated in 3 forms of hyper-IgE syndrome.

Key Words: STAT3, DOCK8, TYK2, T_H17, Job syndrome, Hyper-IgE syndrome, immunodeficiency

SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 SIGNALING

The *STAT3* gene, located on chromosome 17q21, encodes a transcription factor that dimerizes with itself, signal transducer and activator of transcription 1 (STAT1), or STAT4 after cognate receptor activation and translocates to the nucleus to affect transcription in response to multiple cytokines.[1] The interleukin (IL)-6 family members (IL-6, IL-1, IL-31, LIF, CNTF, CLC/CLF, NP, CT1, and OSM), IL-10 family members (IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26), IL-12 family members (IL-23 and IL-27), IL-21, granulocyte colony-stimulating factor, and leptin signal through STAT3.[2,3] Furthermore, STAT3 has been implicated in G protein–coupled receptor signaling and in cellular homeostatic control mechanisms involving mitochondrial regulation of reactive oxygen species (ROS) generation.[4,5] As a result, *STAT3* mutation has the potential for wide ranging effects on the immune system and metabolically active cells, including cancer cells.

STAT3 mutations have been identified in the coiled-coil domain (important for interactions with other proteins), the DNA-binding domains (important for transcriptional regulation), the Src homology 2 (SH2) domains (important in Stat protein dimerization and receptor contacts), and the gene splice sites/trans activation sites (associated with protein interactions important in gene transcription)[6,7] (Fig. 1). Dominant negative mutations in this gene lead to the autosomal dominant form of hyper-IgE syndrome (HIES) (AD-HIES) and a marked reduction in T_H17 cells.[7]

AD-HIES in vitro studies reveal variably impaired neutrophil responses marked by diminished neutrophil chemoattractant receptors FPR, CXCR1, and CXCR2.[8] FPR is a high-affinity receptor for bacterial N-formyl peptides important for neutrophil chemotaxis and microbicidal activity.[8] CXCR1 and CXCR2 receptors are responsive to ELR+ CXC chemokine subfamily members, including CXCL1, 6, 7, and 8.[9–22] In addition to neutrophil trafficking response alterations, signaling to neutrophils is impaired. Minegishi et al[23] demonstrated an inability of T cells to induce skin keratinocyte and bronchial epithelial cell recruitment of neutrophils with anti-staphylococcal molecules, such as CXCL8. Furthermore, a reduction in T_H17 cells can skew adaptive, innate immune system communication responses to *Candida*. T_H17 cytokines, IL-17 and IL-22, regulate antimicrobial peptides, such as histatins and β-defensin-2.[24] Deficits of these antimicrobial peptides may help to explain why saliva from subjects with AD-HIES often has reduced candicidal activity than controls.[24] Additional innate immune response deficits in AD-HIES include altered toll-like receptor (TLR2) responses in the absence of T_H17 cell versus TLR2 signaling in the presence of T_H17 cell responses.[23]

T_H17 cell reduction associated with STAT3 deficiency might be a generalizable phenomenon specific to T-cell differentiation.[25] Siegel et al[25] demonstrated that AD-HIES subjects had decreased central memory CD4+ and CD8+ T cells and increased naive T cells, consistent with a proliferation and differentiation defect from naive precursors. These findings may corroborate with a propensity to develop varicella zoster virus reactivation in AD-HIES.[25]

B-cell dysregulation associated with IgE elevation in HIES is incompletely understood. IL-21 signals through STAT1, STAT3, and STAT5. Studies with naive IL-21 receptor knockout mice demonstrate increased IgE levels but low IgG1 levels.[26] Human in vitro B-cell studies reveal alternative IL-21, context dependent, IgE regulation with low IgE levels in the context of IL-21 incubation with PHA and IL-4, but increased IgE in the context of IL-21 incubation with anti-CD40 and IL-4, suggesting that T-cell–B-cell pathway miscommunication may play a role in IgE elevation.[27] In

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FIGURE 1. Organization of the STAT3 protein.

addition to IgE alterations in AD-HIES, peripheral blood B lymphocytes are skewed toward transitional and naive cells with marked reduction in memory B cells independent of the STAT3 mutation location.[28]

The percentage of peripheral blood memory B cells is frequently reduced in AD-HIES.[29] Furthermore, AD-HIES subjects have defects in peripheral blood memory B-cell subsets, characterized by multiparameter flow cytometry as CD38^{low}CD24^{hi}.[30] Further characterization of cells from this AD-HIES cohort, in comparison with controls, demonstrated decreased numbers of all B-cell subsets, both switched and unswitched with the greatest decrease in the IgA+ switched and IgM+ unswitched memory B-cell populations.[30] Plasma analysis revealed that STAT3-HIES patients had a statistically significant increase in B-cell-activating factor of the TNF family (BAFF), a B-cell survival factor, expression versus controls, which correlated with a decrease in BAFF receptor expression.[30] Furthermore, a positive correlation between National Institutes of Health (NIH) HIES scores and plasma BAFF scores was identified.[30] Most subjects in this cohort also had poor T-cell dependent antibody responses to bacteriophage phiX174 primary and secondary immunizations.[30] The authors comment that these findings reflect both altered B cell–intrinsic and B cell–extrinsic STAT3 signaling defects.[30]

Tissue remodeling proteins are altered in AD-HIES.[31] Matrix metalloproteinases (MMP)-8 (important for contribution to acute lung inflammation and tissue remodeling after acute lung injury) and MMP-9 (important for vascular smooth muscle cell migration, macrophage recruitment and elastin degradation) are elevated 3-fold during periods free from infection in AD-HIES versus controls.[31] Furthermore, MMP-3 (important for cardiovascular matrix remodeling) was lower in AD-HIES subjects versus control subjects.[31]

In a mouse model, Stat3 inactivation in osteocytes and osteoblasts results in bone mechanical alterations, including decreased bone strength, mass, and load response generation, as well as impairment in ROS regulation.[32]

These findings give further validation to previous studies suggesting that STAT3 plays a role in regulating cellular homeostasis through mitochondrial oxidative stress and ROS responses.[4,33]

DEDICATOR OF CYTOKINESIS 8 SIGNALING

DOCK8 is located on chromosome 9p24.[34] Loss of dedicator of cytokinesis 8 (DOCK8) protein function leads to the most common form of autosomal recessive HIES (AR-HIES). DOCK8 is in the family of guanine exchange factors that can activate Rho GTPases, which include ras-related C3 botulinum toxin substrate 1 (RAC1) and cell division control protein 42 homolog (CDC42).[35] Both RAC1 and CDC42 mediate important effects on actin cytoskeletal rearrangements, whereby

CDC42 plays a role in effects at the leading edge of cell remodeling resulting in filopodial protrusions, whereas RAC1 affects lamellipodial protrusions.[36] Rho GTPase family members can affect STAT3 phosphorylation, directly or indirectly (however, these interactions in DOCK8-deficient patients have not been reported to the authors' knowledge).[37–39] *Dock8* deletions have been identified in the Dock homology region 1 (DHR1) domain [important for binding phosphatidylinositol (3,4,5)-triphosphate (PIP3) membrane-rich regions, which assist in perimembrane positional organization] and in the DHR2 domain (important for binding to Rho family GTPases)[40,41] (Fig. 2). Hence, DOCK8, through interactions with Rho GTPases, may play an important role in actin filament arrangement.[40]

B and T lymphocytes express the most DOCK8.[42] Hence, DOCK8-mediated HIES is associated with immunological effects that occur at multiple stages in T- and B-cell development. Findings include reduced CD8+ T-cell stimulation and clonal proliferation.[43] Furthermore, there is a paucity of naive CD8+CD45RA+CCR7+ circulating T cells; to a lesser degree, there is a decline in CD8+CD45RA−CCR7−/+ memory T cells and an increase in a senescent population of effector memory CD45RA+ (T_{EMRA}) cells with the phenotype CD8+CD57+CX3CR1+CD27−CD28−CD127−.[42] Some patients with this condition may have diminished T_H17 cell functional responses; however, these findings do not appear as prominent as in AD-HIES.[44] A mouse model with a DHR2-deficient, homozygous, null DOCK8 allele strain suggests that the most profound T-cell effects are on CD4+ and CD8+ long-lived memory T-cell survival.[45] In a mouse model, B-cell effects include an attenuated ability to form marginal zone B cells and to maintain germinal center B cells with resultant defects in high-affinity antibody generation.[45,46] Engelhardt et al[40] postulate that derangement in cell cytoskeletal organization has the potential to affect immunologic synapse formation.

TYROSINE KINASE 2 SIGNALING

Tyrosine kinase 2 (TYK2) is in the family of Janus kinase molecules, of which there are 4 known in humans. *TYK2* is located on chromosome 19p13.2.[47–49] TYK2 transduces signals transmitted from type I interferon receptors (interferon α and β), cytokine receptors sharing IL-12Rβ1 subunit (IL-12, IL-23), cytokine receptors sharing a gp 130 subunit (IL-6, IL-10, CNTF, LIF, IL-11), and IL-13.[50–58] The TYK2 protein includes a FERM domain (important in localizing the protein to the plasma membrane),[59,60] an SH2 domain (important in modulating regulation of intracellular signaling cascades),[61–64] and a kinase domain (important in phosphorylation of target proteins, such as STAT proteins, which can cause the affected protein to change cellular location or can affect association with other proteins)[65] (Fig. 3).

FIGURE 2. Organization of the DOCK8 protein.

Homozygous deletion mutations have been identified originating in the FERM domain and before the kinase domain in 2 different individuals. In vitro human TYK2-deficient cells, from the FERM origination mutant cells, stimulated with interferon α, did not lead to tyrosine phosphorylation of JAK1, STAT1, STAT2, STAT3, and STAT4.[66] Furthermore, stimulation by IL-6 and IL-10 did not increase SOCS3 levels, a repressor of STAT3.[66] TYK2 deficiency is associated with decreased T_H1 differentiation and increased T_H2 differentiation postulated to be TYK2-regulated IL-12 effects.[66] T-cell replenishment with TYK2 restored IL-12 and interferon α signaling.[66] In a mouse model, impaired TYK2 signaling supported the human impaired T_H1 response findings and demonstrated diminished interferon γ secretion by IL-12–stimulated splenocytes.[67] Impaired T_H1 findings might give further clues to susceptibility to mycobacterial infections in this condition. The mouse model also introduced the notion of impaired IL-17 responses in TYK2-deficient mice by IL-23–stimulated splenocytes, which might explain impaired fungal responses identified in this condition.[67]

CLINICAL PRESENTATION OF AD-HIES

AD-HIES typically presents in the neonate stage marked by papular or pustular rashes that mimic acne, eosinophilic dermatitis, or eczema. Lesions typically begin on the head and scalp before progressing over the rest of the body and frequently become superinfected with *Staphylococcus aureus*, resulting in recurrent abscess formation. These recurrent abscesses are pus filled but lack typical inflammatory responses like warmth, erythema, and pain.[68,69] Viral skin infections are rare in AD-HIES.

Within the first years of life, these patients also get frequent pneumonias with *S. aureus*. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the next most common pathogens. Symptoms include purulent sputum, but fever is typically absent. Infection may lead to lung parenchyma destruction, bronchiectasis, and pneumatocele formation in the majority of affected subjects.[68,69]

Once structural changes occur in the lung, susceptibility to invasive mycotic infections can ensue as reported by Vinh et al.[70] Forty-four percent of patients with structural damage in this cohort contracted at least one such infection.[70] In patients with pneumatoceles and bronchiectasis, *Pseudomonas aeruginosa* and *Aspergillus fumigatus* are frequently implicated pathogens. A study by Melia et al[71] concluded that subjects with lung parenchyma damage have increased

risk of infection by nontuberculous mycobacteria. Rarely, infection progresses to massive hemoptysis.[72]

AD-HIES patients have prominent oral and facial findings that develop from childhood through the teenage years. Findings include facial asymmetry, prominent forehead, broad nose, deep eyes, rough facial skin, and retention of primary teeth, which may cause impaction or a double row of teeth (Figs. 4, 5).

On the hard palate, subjects may have fibrotic bridges that typically run anterior to posterior, which may or may not have associated grooves or clefts. The tongue surface has prominent fissures and a deep midline cleft anterior to the circumvallate papillae is common. This pattern of fissures can also be seen on the lips, cheeks, and mucosa, with prominent keratotic striations.[68] Mucocutaneous candidiasis is also common in affected patients.[69] Salivary gland defects in antimicrobial proteins, β-defensin-2 and histatins, have been attributed to reduced candidacidal responses.[24]

From adolescence onward, the skeletal manifestations of this disorder become prominent. About 75% of HIES teenagers develop scoliosis, which can be severe enough to necessitate rod implantation (Fig. 6).

Severe osteopenia and osteoporosis is common in affected subjects. Frequent fractures of long bones and ribs are reported in approximately 50% of patients. These fractures are not necessarily associated with osteopenia. In the third and fourth decade, degenerative joint disease, often of the spine, can become debilitating and requires surgical correction.[68]

Vascular manifestations of AD-HIES vary in location and severity. Aortic aneurysm rupture has been reported.[73,74] Coronary artery dilation and tortuosity appears common.[75] Specifically, dilation of the left anterior descending coronary artery followed by right coronary artery involvement with prevalences of 51% and 25% was reported by Freeman et al.[75] In contrast, tortuosity appeared more common in the right coronary artery versus the left anterior descending.[75] In this cohort, the findings suggested vessel dilation and tortuosity prevalence increased with age and occurred more often in men.[75] Coronary arteries typically lack evidence of atherosclerotic damage.[76] Other reported vascular abnormalities include patent ductus venosus, pseudoaneurysms, and superior vena cava syndrome.[74] Central nervous system (CNS)–reported abnormalities include vasculitis, leading to a right parietal infarction and thrombosis of the left posterior inferior cerebellar artery.[74]

Gastrointestinal (GI) manifestations of AD-HIES are rare. One case report described a 26-year-old man with sigmoid

FIGURE 3. Organization of the TYK2 protein.

FIGURE 4. Facial features in AD-HIES.

diverticulitis that progressed to a pelvic abscess. Resolution required drainage, intravenous antibacterial and antifungal agents, and sigmoid colectomy for successful treatment.[77] There have been 2 published reports of spontaneous colonic perforations: one occurred in an 18-year-old man who developed cecal perforation and the other involved an 8-year-old girl who

FIGURE 5. Retention of primary teeth in a patient with AD-HIES.

FIGURE 6. Scoliosis in a patient with AD-HIES.

developed transverse colon perforation.[78,79] Three cases of histoplasmosis of the GI tract have been reported. Two occurred in teenage patients thought to have Crohn disease before pathology revealed histoplasmosis and the other occurred in an adult with recurrent colonic histoplasmosis.[80,81]

AD-HIES patients also have an increased risk of developing lymphomas. This risk may be as high as 259-fold over the general population.[82] A review of 23 subjects with lymphoma identified 6 with T-cell lymphomas, 13 with B-cell lymphomas, and 4 with classic Hodgkin lymphomas. Of the B-cell lymphomas, pathologic analysis revealed 6 as diffuse large B-cell lymphomas and 3 as Burkitt lymphomas.[83,84] Other reported lymphomas include peripheral T-cell lymphomas and mantle cell lymphomas.[84]

CLINICAL PRESENTATION OF DOCK8 AR-HIES

Patients with DOCK8 immunodeficiency syndrome (DIDS), the most common form of AR-HIES, have a slightly different presentation from that described above (Table 1). The severe eczema and recurrent skin infections or abscesses caused by *S. aureus* are still prominent, but affected subjects have a higher rate of viral infections, which include molluscum contagiosum, herpes simplex virus, and varicella (Zhang, Englehardt). Food and environmental allergies are common.[40,43] Asthma, eosinophilic esophagitis, and anaphylaxis have also been variably reported.[40,43] Recurrent upper respiratory infections, such as otitis media, otitis externa, and sinusitis, are common, whereas mastoiditis and recurrent croup are rare.[43] Although frequent pneumonias are still common in this group, they typically do not result in pneumatoceles. Implicated lung pathogens include *S. pneumoniae, Haemophilus influenza, Pneumocystis jiroveci, Proteus mirabilis, P. aeruginosa, Cryptococcus*, respiratory adenovirus, and respiratory syncytial virus.[43,85] Mortality from sepsis is much higher in the DIDS patients.

The typical facial presentation of a broad nose, prominent forehead, and facial asymmetry, as well as retention of

TABLE 1. Distinguishing Features Comparing AD-HIES With DIDS and TYK2 HIES

Clinical Finding	AD-HIES	DIDS AR-HIES	TYK2 AR-HIES
Viral skin infections	−	+++	++
Pneumatoceles	++	−	−
Recurrent pneumonia	++	++	++
Sepsis mortality	+	+++	+++
Facial dysmorphic features	+++	−	−
Primary tooth retention	+++	−	−
Scoliosis	++	−	−
Neurologic manifestations	+	+++	++
Cerebral vascular abnormalities	+	++	++
Food allergies	−	+++	−
Environmental allergies	−	++	
Decreased IgM	−	++	−
Atypical mycobacterial infections	−	−	++
Malignancy	+	+++	?
Lymphoma	+	+	?

primary teeth, is absent. Scoliosis is rare in this subset. Mucocutaneous candidiasis is common in DIDS.

There is an increase in neurologic manifestations in DIDS, including facial paralysis, hemiplegia, and CNS vasculitis.[85] Reported CNS infections include JC virus-associated progressive multifocal leukoencephalopathy, and meningitis associated with Cryptococcus and *Haemophilus influenza*.[40,43] Cerebral vascular abnormalities are more common in this group than in AD-HIES.[74] In the CNS, ruptured cerebral aneurysm and subarachnoid hemorrhage have resulted in death before clinical diagnosis, but to our knowledge, this has only been reported twice in the literature in AR-HIES.[85] The discovery of CNS vascular abnormalities may occur incidentally after a stroke or hemiplegia and precipitating features include under-perfusion of large arteries and diminished basal cerebral artery caliber. Aneurysms of the ascending aorta and pericarditis are described affecting the cardiovascular system.[74]

In the GI tract, salmonella enteritis and giardiasis have been reported. Mortality from malignancy is far higher in DIDS than in AD-HIES. Skin-originating cancers are more common and include fatal metastatic squamous cell carcinoma and fatal cutaneous T-cell lymphoma–leukemia.[43] Burkitt lymphoma has been rarely reported.[40] Autoimmune hemolytic anemia has also been reported.[40]

DIDS laboratory findings can reveal, in addition to elevated IgE and eosinophilia seen in AD-HIES, low absolute lymphocyte counts, low total T-cell counts, with low CD4+ and low CD8+ counts but normal CD4+ to CD8+ ratio.[40,43] Neutrophil and monocyte numbers are usually normal, whereas natural killer cell and B cell levels are variable.[40,43] IgG levels can be normal or elevated, IgA levels are variable, IgE levels are typically elevated, and IgM levels are usually low.[40,43]

CLINICAL PRESENTATION OF TYK2 AR-HIES

Two patients with TYK2 deficiency have been reported.[66,86] The 2 patients had homozygous mutations in *TYK2*, but in different locations of the gene. Furthermore, the patients were of different ethnic backgrounds and had varied clinical symptoms. Both patients lacked features typical to AD-HIES, such as skeletal or dental alterations and both patients had susceptibility to intracellular *Mycobacterium bovis* after Bacille Calmette–Geurin (BCG) vaccination, but with variable severity. Both had episodes of cutaneous herpes infection but with variable severity.

The patient with more severe infections was of Turkish descent, had an early termination codon in TYK2 at amino acid position 767 caused by a 9-base pair DNA deletion in exon 16, had mildly elevated IgE (to a maximum of 218 IU/mL), no atopy, asthma, skin candidiasis, boils, folliculitis, or cold abscesses. This patient developed 2 disseminated infections with intracellular organisms. Specifically, 6 months after vaccination with BCG, he was noted to have axillary lymphadenopathy at age 8 months. This infection relapsed after treatment with isoniazid and became generalized at age 21 months, affecting the cervical, axillary, and inguinal lymph nodes bilaterally. Laboratory assessment during chronic infection demonstrated normal nitroblue tetrazolium test, normal serum IgG, IgM, IgA, and mildly elevated IgE. He had no relapse after 18 months of treatment. The patient was subsequently infected at age 8, with the intracellular organism *Brucella* spp after ingestion of unpasteurized cheese. The patient was treated with a 6-week antibiotic course and was found to have neurobrucellosis and pneumonia 1 month later. The patient was severely debilitated after this episode with left temporal, occipital, and bilateral parietal brain infarcts accompanied by sensorineural hearing loss and residual cognitive impairment. At age 11, he had an episode of herpes zoster involving the right maxillary branch of the trigeminal nerve.[86]

The patient with more mild infections was of Japanese descent, had an early termination codon at amino acid position 90 caused by a frame shift mutation at DNA coding regions 70 to 89, had elevated IgE (2100 IU/mL), and susceptibility to viruses, fungi, mycobacteria, and intracellular and extracellular bacteria. He was noted to have atopic dermatitis–like rash in the first month of life, skin abscesses, oral candidiasis, recurrent otitis media, sinusitis, pneumonias, molluscum contagiosum, and herpes simplex infection of the skin and mucosa. He was also noted to develop 2 infections with intracellular infections. The first infection was to BCG at age 22 months. The second infection was to non-typhi salmonella gastroenteritis at age 15. Peripheral blood laboratory assessment revealed normal quantitative T, B, and natural killer cells and normal neutrophil function. In vitro peripheral blood mononuclear cell studies from the patient demonstrated higher basal class I HLA expression, complete defects in type I interferon responses, and failure to make interferon γ after IL-12 stimulation. In vitro studies also revealed blunted IL-6 and IL-10 responses with either absent or attenuated feedback inhibition through suppressor of cytokine signaling (SOCS)3 expression after cytokine stimulation. In vitro studies also revealed increased IL-5 and IL-13 when naive CD4+ T cells were stimulated with IL-2 and anti-CD3.[66]

DIAGNOSIS

Diagnosis of HIES is based on clinical and laboratory findings originally described in a NIH HIES scoring criteria

consisting of 21 features.[87] Although the NIH scale is sensitive for the presence of HIES, it is not specific for the underlying mutation.[88] However, analysis of mutations focused on groups of mutations specifically localized to the STAT3 SH2- and DNA-binding domains, the most common mutation regions, identified that subjects with SH2 domain mutations had a statistically significant increase in scoliosis at a younger age, high palate, increased intertalar distance, and increased otitis and sinusitis.[89] The same cohort had more deaths from infection in subjects with DNA-binding domain mutations versus subjects with SH2-binding domain mutation.[89]

The features identified in the NIH scale that are most suggestive of a *STAT3* mutation include: abscesses of internal organs, other severe infections, pneumatoceles, nail/mucocutaneous candidiasis, bone fractures with minimal trauma, scoliosis, and a family history of HIES.[88] A subject with a family history of HIES and a score >40 points is highly likely to have a HIES genotype, but unlikely if they score less than 20 points.[90] Attempts to refine more sensitive and specific criteria for the diagnosis of specific forms of HIES are ongoing.[88]

Revised clinical guidelines for the diagnosis of STAT3 mutant HIES have been proposed by Woellner et al.[7] A possible diagnosis can be made with IgE levels ≥1000 IU/mL plus a weighted score more than 30 based on 5 clinical findings: recurrent pneumonias, newborn rash, pathologic bone fractures, facial appearance, and high palate. Probable diagnosis would include the above plus a family history of HIES or lack of T_H17 cells, and a definitive diagnosis would require a known *STAT3* mutation.[7] While these clinical predictors have been found useful in better classifying patients with *STAT3* mutations, the features unique to the AR-HIES secondary to *DOCK8* were not addressed.

STAT3 mutation analysis is currently available commercially and used in the research setting, given the large size of the gene and expense of this endeavor. The use of high-resolution polymerase chain reaction–based DNA-melting assays to identify and screen patients for *STAT3* mutations are under investigation.[91] This assay is quicker and cheaper than genomic sequencing and screens for sequence variants by DNA melting point changes. The variants can be subsequently confirmed through targeted sequence analysis, thereby lowering the cost in relation to complete genome sequencing.[91] This technique is reported to have 100% sensitivity in a cohort of 16 patients for the identification of *STAT3* mutations in AD-HIES patients and is expected to identify such mutations in 90% of AD-HIES patients.[91] To date, there is no phenotype/genotype relationship among the numerous *STAT3* mutations identified.[7]

T-cell receptor excision circle (TREC) analysis in newborn screening to detect severe combined immune deficiency identified 3 consanguineous siblings with DIDS to have low TRECs in one sibling and undetectable TRECs in the older siblings aged 4 and 6.[92] These findings raise the possibility for early detection of DIDS and add this condition to the differential diagnosis for absent or low TRECs on newborn screening.

Commercially available tests for diagnosis of DOCK8 and TYK2 deficiency are limited. DIDS diagnostic considerations include assessment for low serum IgM, low T-cell numbers, and low T-cell proliferative responses. DOCK8 and *TYK2* sequencing is available at specialized research laboratories.

TREATMENT

The importance of early recognition and treatment of *S. aureus* and fungal infections is essential as these patients often display fewer of the traditional findings and symptoms associated with these infections.[93] Although skin infections are often treated with anti-staphylococcal antibiotic therapy, antibacterial ointments, dilute bleach, or chlorinated water, recrudescence is one of the classic signs of AD-HIES.[93,94] Viral skin infections in DIDS are challenging and variably responsive to anti-viral therapy. Respiratory infections can lead to lung parenchymal damage; hence, eradication of pulmonary infections is important. Targeted therapy based on culture results could be considered given the risk for antimicrobial resistance with repeated antibiotic exposure. A high index of suspicion for intracellular organism infections could be considered in infections associated with TYK2 deficiency.

Hematopoietic cell transplantation (HCT) has been used in treating both the autosomal recessive and autosomal dominant forms of the disease. Limited information exists regarding long-term outcome; however, many experts recommend transplantation for DIDS, as long-term outcome without transplantation is poor owing to the risk for fatal infections, malignancy risk and CNS infarction, and bleeding.[95] Successful long-term improvement, despite mixed donor chimerism, has been reported in DIDS.[95] Other reports have been mixed. One case study reported successful engraftment with the $CD3^+$ and $CD15^+$ cells being identified as donor 21 days after HCT. After discharge, the subject did not show evidence of any skin infections. Unfortunately, long-term follow-up was unable to be performed as the patient was hospitalized and died 58 days after transplantation due to *Klebsiella pneumoniae* bacteremia. The authors speculate that the transplant recipient's congenital asplenia contributed to morbidity and mortality.[96] Another case series reported the results of HCT on 2 patients with AR-HIES. Although one patient had a complicated transplant course with multiple ulcerative lesions, brain abscesses, and an acute EBV infection after recovery and successful donor stem cell engraftment, both patients demonstrated significant clinical improvement with resolution of their molluscum contagiosum lesions and continued absence of cutaneous viral infections 2 and 4 years after transplantation. Laboratory assessment of the patients' immune function was normal with the exception of low IgA levels in both patients.[97]

Some experts recommend using HCT in AD-HIES patients with malignancy because other disease-related effects can be managed without HCT. The role of HCT in the treatment of AD-HIES is less consistent than reports on patients with DIDS. One case series reported 2 subjects with AD-HIES and non-Hodgkin lymphoma who underwent allogeneic HCT with successful engraftment, and complete donor chimerism was confirmed by $CD3^+$ cell analysis. After transplantation, both subjects demonstrated normalized IgE levels, which remained normal for 14 and 10 years after transplantation, respectively. In addition, neither subject has had

recurrent infections requiring hospitalization, and both have been free of skin infections.[97] Osteoporosis, which was present in one subject, resolved after transplantation. Furthermore, the T_H17 counts were normal.[4] This is in contrast with an earlier report noting the failure of HCT to correct HIES in a patient who relapsed 4 years after transplantation; however, the mutation status of the patient was not addressed in the original article.[98]

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