

Hyper-IgE in the allergy clinic—when is it primary immunodeficiency?

Mark J. Ponsford¹  | Adam Klocperk² | Federica Pulvirenti³ | Virgil A. S. H. Dalm⁴ | Tomas Milota²  | Francesco Cinetto⁵ | Zita Chovancova^{6,7} | Manuel J. Rial⁸ | Anna Sediva² | Jiri Litzman^{6,7} | Carlo Agostini⁵ | Martin van Hagen⁴ | Isabella Quinti³ | Stephen Jolles¹

¹Immunodeficiency Centre for Wales, Cardiff, UK

²Department of Immunology, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic

³Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy

⁴Department of Internal Medicine, Division of Clinical Immunology and Department of Immunology, Erasmus MC, Rotterdam, The Netherlands

⁵Department of Medicine, Treviso Hospital, University of Padova, Padova, Italy

⁶Department of Clinical Immunology and Allergology, St. Anne's University Hospital in Brno, Czech Republic

⁷Faculty of Medicine, Masaryk University, Brno, Czech Republic

⁸Department of Allergy, University Hospital Jiménez Díaz Foundation, Madrid, Spain

Correspondence

Mark J. Ponsford, Immunodeficiency Centre for Wales, Cardiff, UK.
Email: ponsfordm@cardiff.ac.uk

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Abstract

The 2017 International Union of Immunological Societies (IUIS) classification recognizes 3 hyper-IgE syndromes (HIES), including the prototypic Job's syndrome (autosomal dominant STAT3-loss of function) and autosomal recessive PGM3 and SPINK5 syndromes. Early diagnosis of PID can direct life-saving or transformational interventions; however, it remains challenging owing to the rarity of these conditions. This can result in diagnostic delay and worsen prognosis. Within increasing access to “clinical-exome” testing, clinicians need to be aware of the implication and rationale for genetic testing, including the benefits and limitations of current therapies. Extreme elevation of serum IgE has been associated with a growing number of PID syndromes including the novel CARD11 and ZNF341 deficiencies. Variable elevations in IgE are associated with defects in innate, humoral, cellular and combined immunodeficiency syndromes. Barrier compromise can closely phenocopy these conditions. The aim of this article was to update readers on recent developments at this important interface between allergy and immunodeficiency, highlighting key clinical scenarios which should draw attention to possible immunodeficiency associated with extreme elevation of IgE, and outline initial laboratory assessment and management.

1 | RATIONALE AND SEARCH STRATEGY

Half a century has passed since IgE was recognized as the circulating factor responsible for triggering allergic reactions.¹ Its discovery was hampered by its extremely low plasma concentrations, several logarithms lower than other immunoglobulin classes.² A similar challenge exists for the clinician and patient in diagnosing primary immune deficiency, where rarity mandates “*To diagnose PID, you must first think of PID*”.

The adult range for total serum IgE is typically cited as below 100–140 IU/mL,^{2,3} but varies with age⁴ and ethnicity.⁵ Extreme

elevation of IgE levels ten times the upper limit of normal has been used to define the prototypic hyper-IgE syndrome (HIES). Job's syndrome is a triad of elevated IgE, recurrent skin boils and cyst-forming lung infections.⁶ The NIH-scoring system⁷ has been modified and validated² to aid recognition and diagnosis of this autosomal dominant condition; however, it has limited relevance to other PID-associated conditions with extreme elevation of IgE. These include severe combined immunodeficiency (SCID) and other defects in T-cell development, where early recognition is life-saving. There is a wide differential diagnosis for elevated IgE (Table 1). Following a

recent article highlighting medical diagnoses associated with elevated IgE over 1000 IU/mL in a tertiary referral hospital, where the prevalence of primary immunodeficiency was <1%,⁸ we set out to identify distinctive clinical features where pretest probability is sufficient to “think of PID”.

We searched OVID MEDLINE for reports in English available up to 13-2-18 for conditions where IgE values exceeded 1000 IU/mL, in line with the value used within the hyper-IgE-syndrome-screening tool developed by Woellner et al,² using the search terms “primary immune/immunodeficiency,” “PID,” and “hyper OR elevated,” and “IgE” or “Immunoglobulin E” to identify PID syndromes and associated clinical conditions associated with IgE > 1000 IU/mL (Tables 1 and 2). Following expert panel review, we identified five key scenarios which should raise suspicion of rare disease, initial strategies to facilitate safe diagnosis, and management. Scenarios I-IV highlight presentations which should trigger consideration of primary immunodeficiency. Appreciation of allergy as a manifestation of immunodysregulation should also trigger consideration of specialist allergology input for these patients and scenario V considers the relative burden of allergy associated with different disorders. Together these observations provide valuable insights into the pathogenesis of atopy and allergy and serve as a reminder that the finding of an extremely elevated serum IgE remains relevant. Common themes include defects in T-cell receptor signalling, autoimmunity and overlap with connective tissue disease. This can be viewed in addition to well-known warning signs of PID, such as family history of severe recurrent infections, consanguinity or unexplained death.⁹

2 | I: NEONATAL ERYTHRODERMA

Erythroderma is a medical emergency defined as inflammatory skin disorder affecting more than 90% of the body surface.¹⁰ Although uncommon in children, erythroderma may be the clinical presentation of a wide range of acquired and inherited diseases, including infections, inflammatory skin diseases, inborn errors of metabolism, ichthyoses, drug hypersensitivity reactions and congenital immunodeficiencies. Onset within the first month of life often heralds an underlying monogenetic cause.¹¹ Rapid diagnostic assessment in

parallel with supportive measures is vital to differentiate infective or iatrogenic causes (e.g drug related), and direct appropriate treatment. Skin biopsy with H&E and immunohistochemistry are invaluable in differentiating the underlying cause,¹⁰ enabling nature of dermal inflammatory infiltrate to be determined alongside characteristic epidermal changes. Typical features may not develop until after 6 weeks of age.¹² In this setting, demonstration of exaggerated total IgE alongside eosinophilia can help narrow the differential diagnosis (Figure 1) and should prompt consideration of atypical presentations of severe combined immunodeficiency (SCID) with Omenn syndrome. This is characterized by early-onset diffuse exudative erythroderma, alopecia, lymphadenopathy, hepatosplenomegaly, chronic persistent diarrhoea, failure to thrive with hypereosinophilia and serum IgE levels reported in excess of 10 000 IU/mL.¹³ Omenn syndrome was first described in association with hypomorphic mutations in RAG1 and RAG2; however, mutations in other SCID genes are now recognized. ADA-SCID appears particularly associated with elevated IgE levels.¹⁴ Bone marrow transplantation in this setting is a medical emergency and is life-saving.

An Omenn-like syndrome can also be the first manifestation of complete DiGeorge syndrome and may be accompanied by hypocalcaemic tetany, cardiac and palatal defects. Thoracic imaging may demonstrate thymic absence. Complete DiGeorge syndrome represents 1.5% of patients with 22q11 deletions and may present with an Omenn-like syndrome. Thymic transplant is successful in restoring peripheral lymphocyte function, but immunosuppression may be required to prevent graft rejection and post-transplant autoimmunity.¹⁵

Barrier defects also manifest with severe early onset of cutaneous features in association with failure to thrive, infection and extreme elevation of serum IgE. The commonest keratinization disorder, ichthyosis vulgaris, is caused by loss-of-function mutations in filaggrin (FLG). Null mutations are now recognized as the most common genetic risk factor for development of atopic sensitization; however, their penetrance is incomplete.¹⁶ Comèl-Netherton syndrome (CNS) is a distinctive congenital ichthyosis syndrome, caused by highly penetrant autosomal recessive mutations in the serine protease inhibitor gene Kazal-type 5 (SPINK5) which plays a central role in preserving skin barrier integrity. The initial presentation of CNS is

TABLE 1 Differential diagnosis of elevated IgE

Disease Group	Examples
Atopic disease	Atopic dermatitis, allergic asthma, allergic rhinitis/conjunctivitis
Parasitic infection	Helminths (e.g Ascaris, Enterobius, Schistosoma, Strongyloides)
Viral infection	Human immunodeficiency virus (HIV)
Malignancy	Hodgkin and Non-Hodgkin lymphoma, Sézary disease, IgE multiple myeloma
Lung diseases	Allergic bronchopulmonary aspergillosis (ABPA), Chronic eosinophilic pneumonia
Primary immunodeficiencies	IUIS recognized hyper-IgE syndromes • Autosomal dominant loss-of-function STAT3 • Autosomal recessive PGM3 deficiency • Autosomal recessive SPINK5 deficiency See Table 2

TABLE 2 PID conditions associated with serum IgE > 1000 IU/mL

PID defect associated with IgE > 1000 IU/mL				Section				
Altered process	Genetic defect	Functional defect	Inheritance	I: Erythroderma	II: Infantile eczema and recurrent infections	III: Syndromic features	IV: Autoimmunity	V: Allergy
Barrier-defect	SPINK5 "Cornel-Netherton Syndrome"	Defective epidermal LEKTI protein ¹⁸	AR	Erythroderma/Omenn-like syndrome	Severe dermatitis Predominantly cutaneous infection	-	-	Prominent
	TRPV3	Thermosensitive cation nonselective channel in skin and immune cells ²¹	AD/AR					
	DSG1 "SAM syndrome"	Loss of desmoglein compromises epidermal integrity and barrier function ²²	AR					
	FLG	Loss of filaggrin compromises epidermal integrity and barrier function ¹⁶	AR					
	CDSN	Loss of corneodesmosin compromises epidermal integrity and barrier function ¹⁰³	AR					
Restricted T-cell repertoire ^a 13,14	ADA deficiency	Elevated lymphotoxic metabolites	AR	Erythroderma/Omenn-like syndrome	Opportunistic infections (bacterial, viral, fungal)	Syndromic features may be present (e.g. 22q11ds)	Variable	Variable
	CHD7	Chromatin organization defects	AR					
	DNA Ligase IV	Double strand break repair	AR					
	IL-2R γ	Defective in common γ -chain of multiple cytokine pathways (IL-2/4/7/9/15)	XL					
	IL-7R α	Defect in IL-7 cytokine signalling	AR					
Impaired TCR signalling and cytoskeletal remodelling ^a	RAG1/2	T- and B-cell receptor generation abnormality	AR					
	ZAP70	TCR transduction signalling defect	AR					
	Atypical 22q11 deletion syndrome	Complete athymia with DiGeorge Syndrome ¹⁵	AD					
	WAS	Regulates Arp1/2 complex ⁷²	XL	Early-onset eczema	Severe eczema with opportunistic infections	(Thrombocytopenia)	Prominent (see Table 3)	Prominent
	DOCK8 deficiency	Regulates cdc42 and WASp activation ^{46,50}	AR					
	ARPC1B deficiency	Component of Arp2/3 complex required for f-actin polymerization ⁴²	AR	-	Transient dermatitis Bacterial skin and gut infections	Thrombocytopenia	Inflammatory gastrointestinal disease	Present
								(Continues)

(Continues)

TABLE 2 (Continued)

PID defect associated with IgE > 1000 IU/mL					Section			
Altered process	Genetic defect	Functional defect	Inheritance	I: Erythroderma	II: Infantile eczema and recurrent infections	III: Syndromic features	IV: Autoimmunity	V: Allergy
	MALT1	Scaffold in CBM signalosome with paracaspase activity ⁵¹	AR	Early-onset rash	Persistent dermatitis Cutaneous and pulmonary infections	Low impact fractures	Inflammatory gastrointestinal disease	-
	CARD11 (hypomorphic)	Defective activation of NF- κ B and mTORC1 kinase pathways ⁵⁰	AD	-	Severe atopic dermatitis Variable infections beyond skin	-	-	Prominent
Defective glycosylation	PGM3	Defective glycosylation ^{37,38}	AR	-	Severe atopic dermatitis	Neurodevelopmental delay	-	-
Cytokine signalling defects ^a	STAT3 "Job's syndrome" ZNF341	Defective STAT3 signalling with disruption of wide range of intracellular pathways ³² Key upstream regulatory step needed to trigger the normal induction of the Th17 differentiation pathway ^{34,35}	AD AR	Early-onset rash	Distinctive dermatitis pattern Staphylococcal abscesses Pneumatoceles	Distinctive facial, vascular, & skeletal features	-	Increased
	TGF- β /R/SMAD "Loeys-Dietz Syndrome" ERBIN	Deregulated TGF- β signalling with increased regulatory T cells and total FOXP3 expression ^{62,63}	AD	-	Dermatitis common Infection not prominent	Similar to STAT3	-	Increased
	STAT5b ^{GOF}	Somatic mutation driving nonclonal eosinophilia ⁵⁸	Somatic	-	Early-onset urticaria, dermatitis Variable infections	-	Alopecia totalis	Variable
	IRAK4 MYD88	Defective IL-1 receptor (IL-1R) and TLR signalling (except TLR3) ⁸⁸	AR	-	Eczema uncommon Recurrent life-threatening bacterial diseases with blunted inflammation	-	-	-
	IL6ST	Encodes gp130, common subunit for IL-6, IL-11, IL-27, and OSM receptor signalling ⁶⁴	AR	-	Eczema Recurrent skin and pulmonary infections	Craniosynostosis Neurodevelopmental delay	-	-
	TYK2	Defective cytokine signalling type I and II cytokines ^{54,55}	AR	-	Recurrent bacterial, viral, and mycobacterial susceptibility	-	-	-
Tolerance failure ^a	FOXP3 "iPEX"	Defective generation of regulatory T cells ⁶⁷	XL	Severe early-onset dermatitis Recurrent severe infections	(Lymphoproliferation)	Prominent (see Table 3)	Variable	
	FAS/FAS-L, caspases 8 and 10 "ALPS"	Defective apoptosis including rogue germinal centre B-cell maturation ⁷⁰	Usually AR	-	Bacterial infections associated with neutropenia	(Lymphoproliferation)	Prominent (see Table 3)	-

(Continues)

TABLE 2 (Continued)

PID defect associated with IgE > 1000 IU/mL					Section			
Altered process	Genetic defect	Functional defect	Inheritance	I: Erythroderma	II: Infantile eczema and recurrent infections	III: Syndromic features	IV: Autoimmunity	V: Allergy
Congenital defects of phagocyte	-CYBB- gp91 - NCF1 (p47phox), NCF2 (p67phox), CYBA (p22phox), and NCF4 (p40phox)) "CGD"	Defects of nicotinamide dinucleotide phosphate (NADPH) oxidase components ⁹⁶	XL AR	-	Bacterial and fungal infections (invasive). Atopic dermatitis not prominent.	-	Inflammatory gastrointestinal disease	-
Polygenic disorders	Selective IgA deficiency	Impaired mucosal/barrier defence ⁹²	-	-	Often asymptomatic	-	-	-

"-" denotes presentation is not reported or observed in case reports/series.

^aPathway defects may overlap in practice.

with early-onset generalized rash that develops into severe ichthyosis.¹⁷ Characteristic bamboo hair (*trichorrhexis invaginata*) is often present.¹⁸ CNS presents at the interface of PID, with impaired vaccine responses, particularly to polysaccharide T-cell independent vaccines. Prognosis is poor, with up to 20% mortality at one year. Laboratory testing shows hypoalbuminaemia and electrolyte imbalances due to skin failure, enteropathy, with a resulting failure to thrive. Conventional supportive therapy should include allergy control and skin care (emollients, topical steroids, calcineurin inhibitors, retinoic acid and antibiotics) alongside nutritional and electrolyte support. These can improve but may not normalize skin fully (Figure 2). Assessment of T-dependent and T-independent vaccination responses may support trial of immunoglobulin replacement therapy (IGRT), which has been associated with remarkable clinical benefit.¹⁸ Anti-TNF- α therapy and omalizumab have also been used with benefit in small series in CNS.^{19,20} Recognition of CNS within the IUIS-PID classification of HIES¹⁸ raises the question whether other barrier defects may be associated with immune deficiency. Olmsted syndrome is caused by constitutive activating mutations of TRPV3 and is characterized by mutilating palmoplantar keratoderma, dermal infections, eosinophilia and gross elevation of IgE.²¹ Desmoglein-1 deficiency has been recognized as a rare autosomal recessive disorder associated with severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome. Erythroderma manifests within the first weeks of life and may be complicated by recurrent life-threatening infections, notably respiratory and skin. Food allergy and elevated IgE follow barrier dysfunction and enhanced systemic Th2 response.²²

3 | II: INFANTILE ECZEMA AND RECURRENT INFECTIONS

Eczematous lesions are the second most common cutaneous presentation of PID after infections.²³ Recognition is challenging as atopic dermatitis (AD) affects up to 20% of populations from developed countries, typically manifesting during childhood after 2 months of age.²⁴ Individuals with severe AD often show greatly increased IgE levels and eosinophilia and are at risk of suprainfection with *S. aureus*, *Herpes simplex* or *Molluscum contagiosum*.²⁵ Detailed exploration of the timing and nature of dermatitis can be informative. In a case series of patients with clinical diagnoses of HIES, 8 of 43 were born with a rash; 81% had developed the rash within the first 35 days of life.²⁶ STAT3-LOF mutations were subsequently confirmed in these patients (personal communication, B Grimbacher).

Patients with severe AD appear highly enriched for underlying PID, with Aghamohammadi et al²⁷ identifying six of 75 patients through a combination of history, clinical and laboratory findings; ideally, molecular confirmation should be performed to support diagnosis (outlined Figure 3). Dermatitis is also a common presenting feature of some autoimmune disorders, such as the immunodysregulation, polyendocrinopathy and enteropathy X-linked (IPEX) syndrome.²⁸ These observations underline the importance of eliciting a

personal or family history of recurrent infections in patients with dermatitis, as recognition of a PID disorder can provide additional or curative therapeutic options.

The nature of dermatitis can also aid diagnosis. The prototypic hyper-IgE syndrome, Job's syndrome (STAT3 loss of function), is characterized by recurrent staphylococcal skin abscesses, chronic mucocutaneous candidiasis and pneumonia. In addition to early onset, skin findings distinguishing it from atopic dermatitis include distinctive thickened texture of the facial skin, retroauricular fissures, and severe folliculitis of the axillae and groin. Chronic mucocutaneous candidiasis may also be present.²⁶ Although defective neutrophil chemotaxis has been described,²⁹ aspiration of "cold" abscesses often reveals frank pus.³⁰ Analysis of the skin microbiome for patients with STAT3-HIES reveals a distinctive microbiome to healthy individuals, with bacterial and fungal species such as *Clostridium* and *Serratia marcescens*, *Candida*, and *Aspergillus*.²³ The significance of early diagnosis follows recurrent sinopulmonary infections by encapsulated bacteria and *Staphylococcus Aureus* observed within the first year of life. These often lead to pneumatocele formation, creating a focus for subsequent opportunistic pathogens (Figure 4). Early instigation of prophylactic antistaphylococcal and

antifungal agents is recommended to reduce risk of cutaneous and sinopulmonary bacterial infections, alongside topical antiseptics.³¹ Variable specific antibody production is seen, and patients may require immunoglobulin replacement.

The molecular cause of Job's syndrome was elucidated in 2007 as autosomal dominant mutations in STAT3 causing loss of function.³² This is integral for a number of immunological processes including differentiation of IL-17/22 producing Th17 effector T cells, which in humans play a key role in controlling infections due to extracellular fungi.³³ ZNF341 deficiency has recently been identified as an autosomal recessive cause of this phenotype, highlighting a role for this transcription factor in modulating STAT3 nuclear localization and transcription.^{34,35} STAT3 deficiency is amenable to allogeneic haematopoietic transplantation, although longer-term follow-up is required to establish the degree of phenotype reversal given the wider functions regulated by STAT3³⁶—as discussed in section III.

Autosomal recessive phosphoglucomutase 3 (PGM3) deficiency was described in 2015, linking defective glycosylation with multisystem involvement some replicating features of STAT3-HIES.³⁷ Neurological symptoms in early infancy are distinctive additions to an

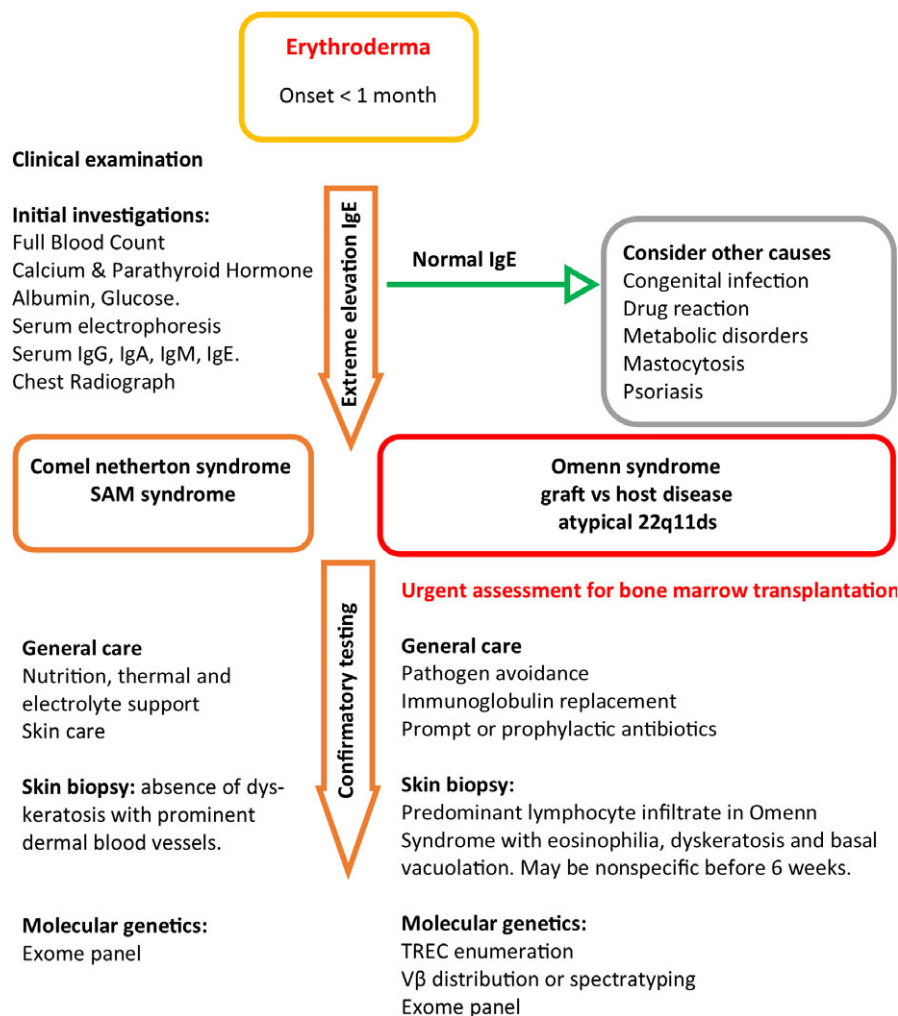


FIGURE 1 Approach to child with erythroderma: considering PID-related differential diagnosis



FIGURE 2 Comel-Netherton syndrome. Photographs obtained by TM with parental consent and subject assent

infective and atopic phenotype. These include developmental delay, psychomotor retardation, hypotonia, ataxia, dysarthria, sensorineural hearing loss and myoclonus. Skeletal abnormalities may resemble those of STAT3-HIES patients.³⁷ Leukocytoclastic vasculitis is a distinguishing feature but is not universally present. Defective glycosylation may also compromise antibody function due to aberrant post-translational modification. PGM3-deficiency patients display susceptibility to bacteria, fungal and viral infections, representing an overlap between STAT3 and DOCK8 (as described below) patterns of infection.³⁸ Pneumatoceles have been considered pathognomonic for STAT3-HIES; however, they are now recognized to accompany other PIDs including PGM3-deficiency.³⁸

When severe eczema is associated with recurrent viral infections, combined immunodeficiency syndromes should also be considered.³⁹ DOCK8 and WAS protein both play a critical role in the initiation of T-cell receptor-driven actin polymerization and interact via a complex also involving WIP,⁴⁰ integrin regulator *talin*⁴¹ and Arp2/3 complex.⁴² The integrity of the actin cytoskeleton is important for T-cell migration into tissues, defence against pathogens, with defects in epithelial immunosurveillance contributing to viral persistence and increased rates of haematological and dermatological malignancy.⁴³ Weak TCR signalling during T-cell activation has been associated with a skew towards the development of T helper type 2 cells (Th2 cells),⁴⁴ suggesting its status as a default differentiation pathway partly underlying the features of atopy in these patients.

DOCK8 deficiency is inherited in an autosomal recessive fashion, and suspicion should be raised where there is a background of consanguinity. It shares many clinical features with STAT3-HIES, including eosinophilia, staphylococcal skin and respiratory infections. Whilst survival until the sixth decade is common for individuals with STAT3-HIES, median survival in DOCK8 is typically only 20 years despite prophylactic antimicrobials and immunoglobulin replacement.⁴⁵ This places emphasis on early diagnosis to direct potentially curative allogeneic bone marrow transplantation, ideally prior to development of end-organ damage or disability.⁴⁶

WASp deficiency, which results in the X-linked WAS, shares clinical features of viral skin infections, recurrent sinopulmonary infections, eczema, elevated serum IgE levels, food allergies and an increased risk for malignancy and autoimmune diseases. Early suspicion of Wiskott-Aldrich syndrome should be raised by the triad of eczema within the first weeks of life, thrombocytopenia with small platelets (<6 fL) and recurrent infections; however, the complete triad is present in only one-third of cases.⁴⁷ Skewed X-inactivation can result in symptomatic females.⁴⁸ The eczema resembles classical AD, but may be more severe and combined with serosanguinous crusting, petechiae and purpura.⁴⁹ Encapsulated bacteria account for most infective episodes, but *Pneumocystis jirovecii* or disseminated herpes simplex and varicella viral infections are also prominent. Malignancies, typically EBV-positive B-cell lymphoma and leukaemia, are common.⁴⁷ Homozygous defects in a component of the Arp2/3 complex have been described in a child with combined immunodeficiency, mild bleeding tendency, elevated IgE and multiple allergies.⁴²

The recent landmark description of hypomorphic mutations in CARD11 as a novel autosomal dominant cause of hyper-IgE, associated with AD and variable skin and lung infective phenotype, highlights the potential for personalized therapy through molecular diagnosis. CARD11 has also been identified as a risk locus for AD.⁵⁰ The mutation causes a dominant-negative effect, disrupting the CARD11-Bcl2-MALT1 (CBM)-signalosome. Autosomal recessive MALT1 insufficiency associated with chronically elevated IgE is also reported.⁵¹ Exploration of the molecular pathway highlights glutamine signalling via the CBM-mTOR pathway as a key driver to polarization of naïve T cells to a Th1/17 fate⁵²; loss of CARD11 results in a Th2 bias, which can be ameliorated in vitro by glutamine supplementation.⁵⁰

Randomized clinical trials of glutamine supplementations in very low-birthweight infants have demonstrated a reduced incidence of atopic dermatitis in the first year of life.⁵³ Future evaluation of dietary glutamine supplementation in atopic individuals (including with

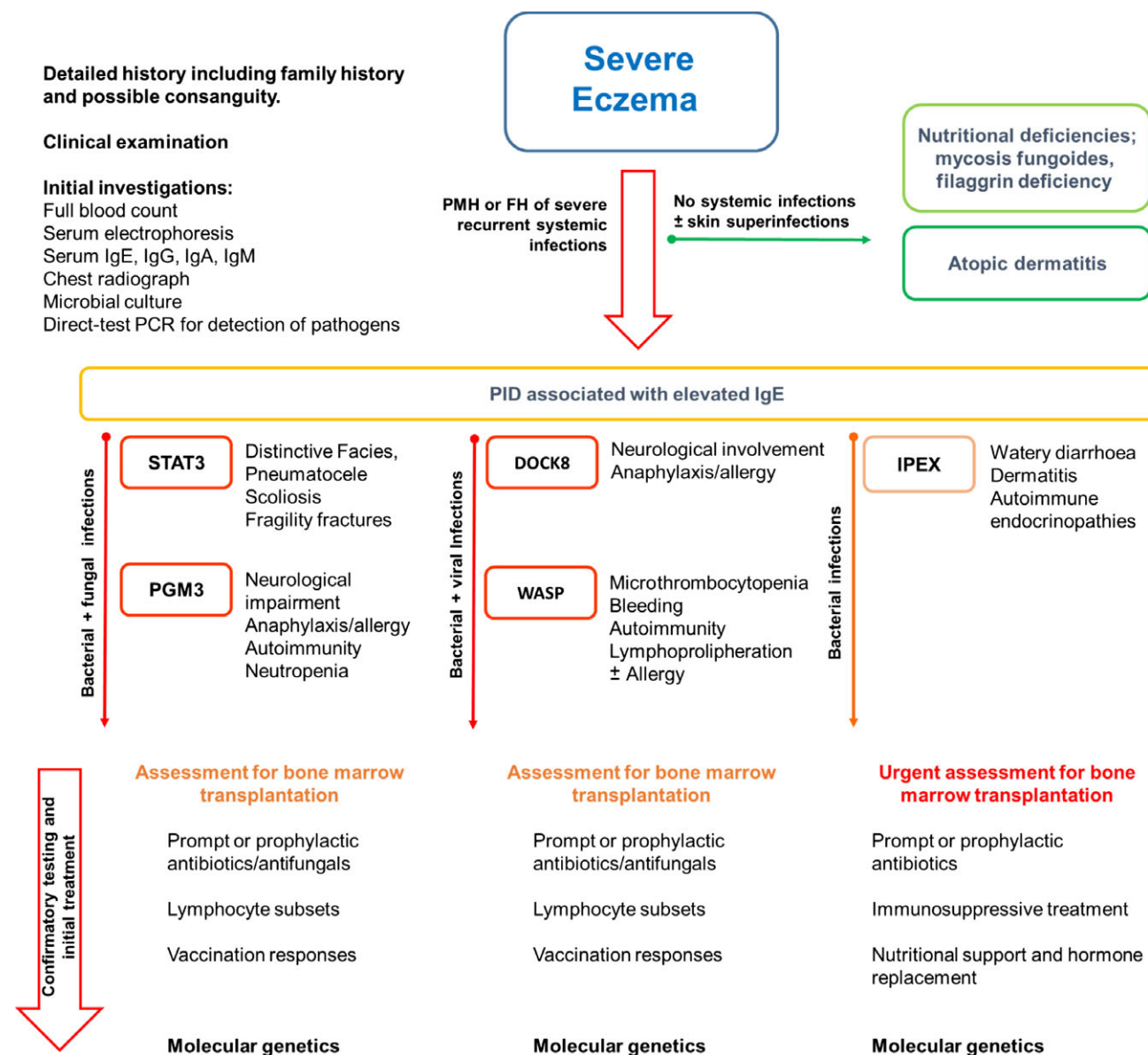


FIGURE 3 Approach to child with severe eczema and possible PID-related diagnosis

CARD11-mutations) is suggested to assess whether this simple dietary manoeuvre can lead to real benefit in vivo.

Among PIDs associated with IgE elevation and eczema in childhood, autosomal recessive mutations in nonreceptor tyrosine kinase 2 (Tyk2) have classically been labelled as a HIES, based on the initial case description of patients who suffered from AD⁵⁴; however, the subsequently identified patients have failed to recapitulate the atopic phenotype.⁵⁵ Similar observations have been made for mammalian sterile 20-like one deficiency, a rare form of combined immunodeficiency, where high IgE levels were found only in three of 10 patients described to date.⁵⁶ Recessive defects in the cytoskeletal regulator CARMIL2 manifest with dermatitis and combined immunodeficiency, but only two of seven patients had IgE >1000 IU/mL.⁵⁷ A novel somatic STAT5b gain of function has been associated with nonclonal eosinophilia, atopic

dermatitis, urticaria and diarrhoea in two paediatric patients; however, serum IgE was only elevated in one.⁵⁸ Consequently, it is difficult to separate mechanistic links to incidental background atopy.

4 | III: SYNDROMIC APPEARANCE OR CONNECTIVE TISSUE DISORDER

A hallmark of STAT3-HIES is its multisystem nature, encompassing a range of dental, craniofacial, musculoskeletal and vascular abnormalities that represent nonimmunological complications of the dominant-negative STAT3 mutation,³ (Figure 5). These features may be absent early in life, and their manifestation can have significant implications beyond diagnosis. Minimal trauma fractures

occur in over half of patients; fracture risk is disproportionate to the degree of osteopenia, suggesting conventional measures for improving bone density via inhibition of osteoclastogenesis may be ineffective.⁵⁹ Screening of adult STAT3-deficient patients with multimodal angiography demonstrated arterial abnormalities of peripheral and brain circulations in 84% and coronary arteries in 50%.⁶⁰ These represent a hidden and potentially devastating complication of this disorder and should be considered in the diagnostic assessment of patients.⁶¹

A connective tissue and atopic phenotype with variable elevation of IgE are also observed in Loeys-Dietz syndrome (LDS). Here, autosomal dominant mutations in the transforming growth factor β (TGF- β) receptor pathway are associated with a Marfan-like syndrome and familial thoracic aortic aneurysms. Affected individuals have a high prevalence of allergic presentations, including asthma, food allergy, allergic rhinitis, atopic eczema and eosinophilic gastrointestinal disease.⁶² The molecular link between nonimmunological connective tissue phenotypes and allergic diseases has recently been revealed by description of ERBIN deficiency. ERBB2-interacting protein (ERBIN) is integral for STAT3-mediated downregulation of TGF- β signalling. Loss of ERBIN favours regulatory T-cell (T-reg) and Th2 polarization, recapitulating the allergic and connective tissue phenotypes of LDS and STAT3-HIES.⁶³ Homozygous mutation of IL6ST (encoding GP130) has recently been described in a patient presenting with eczema, recurrent infections, bronchiectasis, high IgE, defective B-cell memory. They showed an impaired acute-phase response, as well as skeletal abnormalities including craniosynostosis. GP130 acts as the common subunit for cytokine receptor for multiple cytokines, and deficiency leads to blunting of interleukin 6 (IL-6), IL-11, IL-27 and oncostatin M signalling.⁶⁴ It is intriguing to note case reports of craniosynostosis in association with HIES, prior to description of many of these genes⁶⁵; consequently, the true incidence of these mutations is likely underreported due to their novelty.

5 | IV: AUTOIMMUNITY

The presence of autoimmunity in association with elevated IgE is a hallmark of several primary immunodeficiencies. Principal among these are two dysregulation syndromes: IPEX and ALPS (autoimmune lymphoproliferative syndrome), which serve as paradigms for defects of central and peripheral tolerance. Prevalence of autoimmune complications in these select PIDs is summarized in Table 3, with patients commonly developing multiple autoimmune complications.

First described in 1982 by Powell et al,⁶⁶ IPEX is caused by a defect in the *FOXP3* gene, which is vital for development and function of thymic-committed T-regs. Symptoms appear during the first months of life and are characterized by potentially life-threatening enteropathy presenting as intractable diarrhoea and eczema of variable severity. Patients develop early-onset autoimmune disorders, typically type 1 diabetes, autoimmune thyroiditis or nephritis.⁶⁷

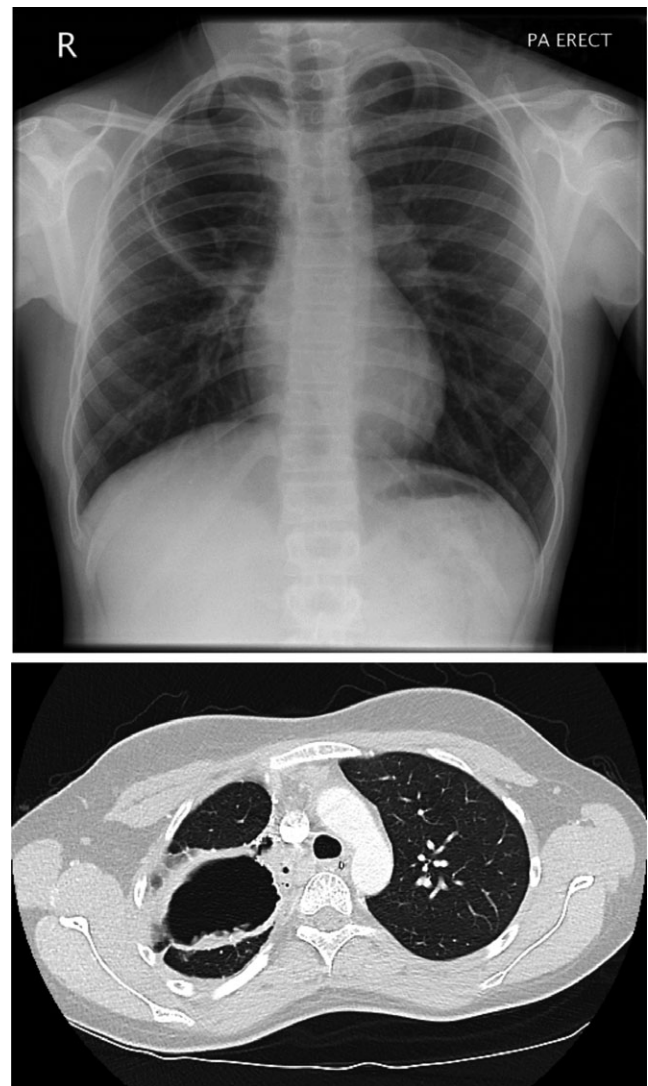
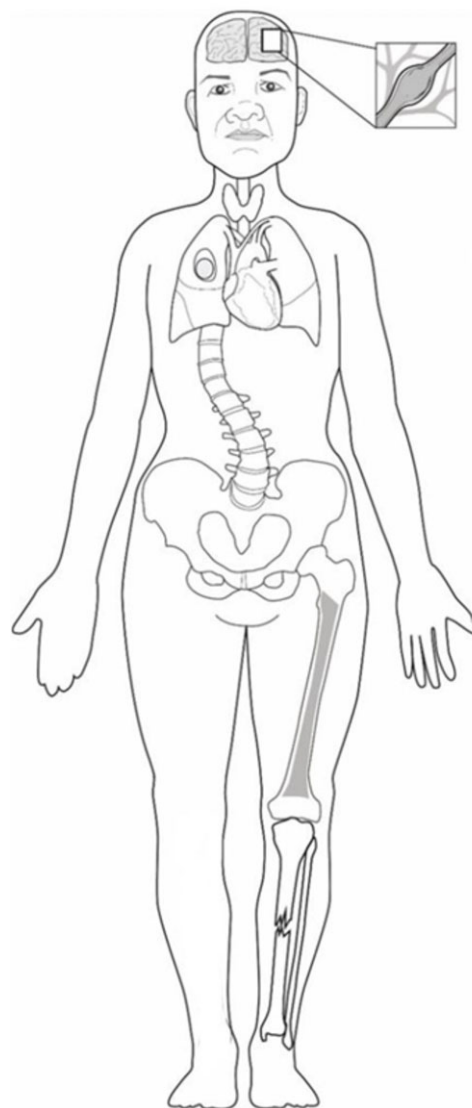


FIGURE 4 Chest radiograph and computed tomography (CT) images of right upper lobe pneumatocele in a STAT3-HIES patient, developing by age 19 following recurrent pneumonias

Aside from elevated IgE, detailed immunological profiling in IPEX demonstrates normal lymphocyte numbers and immunoglobulins, but absent CD4⁺CD25^{hi}FOXP3⁺ Tregs.⁶⁸ Molecular diagnosis is confirmed by identification of *FOXP3* mutations, although homozygous mutations in *CD25* may phenocopy IPEX.⁶⁹ Treatment relies on immunosuppression as a bridge to HSCT. Gene therapy to produce Treg-like cells from IPEX patient CD4⁺ lymphocytes may hold promise.

ALPS is caused by heritable defects in lymphocyte apoptosis ("including" Fas, Fas-ligand, caspase-8, caspase-10, or undefined), resulting in failure of lymphocyte negative selection leading to the survival of autoreactive T and B cells. Elevated serum IgE levels and eosinophilia are observed in 16%-25% of patients with ALPS, likely caused by antigen-independent maturation of IgE-producing class-switched plasma cells.⁷⁰ Clinically this manifests with chronic nonmalignant lymphadenopathy, splenomegaly and autoimmunity—in particular cytopenias (autoimmune haemolytic anaemia, thrombocytopenia,

Autosomal Dominant STAT3-Loss of Function



Vascular: Aneurysms and ectasia.

Facial dysmorphism: Coarse features, asymmetry, broad nasal root, hypertelorism, prognathism. Retained primary dentition, high-arched palate

Infective:

Bacterial: Sinopulmonary and cutaneous: staphylococcus aureus, streptococcal pneumoniae, haemophilus, klebsiella.

Fungal: Chronic mucocutaneous candidiasis, pneumocystitis jiroveci.

Viral: VZV reactivation.

Pneumatocoele formation and secondary infection with pseudomonas aeruginosa, atypical mycobacteria or aspergillus.

Gastrointestinal: GI dysmotility, reflux, eosinophilic oesophagitis.

Musculoskeletal: Scoliosis, minimal impact fractures, osteopenia, joint hyperflexibility.

FIGURE 5 Diagram showing syndromic features of AD-HIES.

Courtesy of Cardiff University Medical Illustration Department

neutropenia). There is an increased risk of haematologic malignancies, in particular lymphoma.⁷¹ Laboratory findings of an elevated population of double-negative (CD4[−]8[−]) TCR-alpha/beta cells and elevated serum vitamin B₁₂ should alert clinicians to the possibility of ALPS. Treatment options include corticosteroids and high-dose intravenous immunoglobulins, as well as immunosuppressive and immunomodulatory agents, such as rituximab, mycophenolate mofetil, calcineurin inhibitors or sirolimus.

Rates of autoimmune complications are also increased in both WAS and DOCK8, affecting almost 26%–72% of patients WAS^{72,73} and 13% of DOCK8 patients.⁴⁶ Typically this manifests in the form of a vasculitis or an autoimmune haemolytic anaemia (AIHA).⁴⁶ Patients with the milder X-linked thrombocytopenia may also develop autoimmunity over time, notably IgA nephropathy.⁷⁴ Early haematopoietic stem cell transplantation has become the standard of care for children with these disorders. In WAS at least, the level of donor chimerism is a powerful predictor of post-HSCT autoimmunity, malignancy or thrombocytopenia.⁷⁵ This is an important outcome to

consider for future gene therapy trials, where full chimerism may be difficult to achieve.

Conditions including inflammatory bowel disease or discoid lupus may accompany neutrophil function defects such as chronic granulomatous disease (CGD). Case series linking CGD with marked elevations of IgE and sensitization to *Aspergillus* species highlight overlap and possible confusion with allergic bronchopulmonary aspergillosis (ABPA). The use of steroid monotherapy for “ABPA” in undiagnosed HIES or CGD cases has led to invasive disease and mortality.⁷⁶

6 | V: ALLERGIC MANIFESTATIONS OF PID

Elevation of serum total IgE is characteristic but not specific for allergic diseases. Total levels at birth correlate poorly to future allergy⁷⁷; however, elevation in young children is associated with subsequent development of allergen-specific IgE and allergic disease, particularly respiratory.⁷⁸ Misdiagnosis of PID as allergy is well described and may be

complicated by co-occurrence of allergy as a manifestation.⁷⁹ Comparison of sensitization patterns shows marked differences between patients with DOCK8, STAT3 or AD.⁸⁰ Allergic symptoms and skin prick test results correlate well with specific IgE results in DOCK8 and AD patients⁸⁰ and can be useful in directing dietary exclusion.⁸¹ In an international review of 136 cases, over 70% of DOCK8 patients had clinical symptoms of allergy, with food-related anaphylaxis in 16%. Drug allergy, asthma and rhinitis were also observed.⁴⁶ Food allergy in DOCK8-HIES patients can persist even following HSCT despite full donor chimerism.⁸² Multiple allergies are reported in the limited published series of PGM3-HIES,³⁷ whilst WAS patients and murine models frequently develop IgE-mediated reactions to common environmental and food allergens.⁸³

In contrast, STAT3-HIES patients show remarkably similar specific IgE values and skin prick testing to healthy individuals despite extremely high total IgE levels.⁸⁰ The lifetime frequency and severity of food allergies for STAT3-HIES remain higher than reported by healthy controls but is greatly diminished relative to atopic controls with similar IgE.⁸⁴

One explanation for this apparent paradox is the profound impairment of mast cell degranulation associated with STAT3 loss of function.⁸⁴ Physicochemical analysis of the skin barrier in STAT3-HIES and AD individuals suggests an additional explanation: dermal integrity remains remarkably preserved in STAT3-HIES.⁸⁵ In contrast to atopic dermatitis patients, transepidermal water loss (TEWL) and stratum corneum thymic stromal lymphopoietin (TSLP) were equivalent to healthy controls in STAT3-HIES.⁸⁵ This is in line with the observation that topically applied JAK inhibitors ameliorate eczema, acting through suppression of STAT3 signalling to enhance filaggrin expression.⁸⁶ Assessment of TEWL presents a useful bedside tool to risk stratify babies at risk of future atopic dermatitis⁸⁷ and can direct more aggressive supportive therapy.

Discordance between total IgE and allergic symptoms is not exclusive to STAT3-HIES. Mutations within innate-immune signalling pathways including IRAK4 and MyD88 have been described in association with a hyper-IgE like syndrome. In a case series of 48 IRAK4 patients and 12 MyD88 patients, none of these patients were reported to suffer from allergic asthma, whilst chronic eczematous skin disease was reported only in one patient.⁸⁸ However, a variety of allergen-specific IgE are detectable in a subset of patients with MyD88 and IRAK4 deficiencies,⁸⁹ and disruption of effector responses might also contribute. Similarly, despite elevated circulating IgE levels and eosinophilia in a subset of patients with ALPS, the prevalence of allergic diseases does not appear increased.⁷⁰ This subset of patients is noteworthy, however, as they represent a distinct subgroup of ALPS patients with higher mortality from infectious complications.⁹⁰

Allergic diseases may be the first and/or only clinical manifestation of selective IgA deficiency, sIgAD. This is the commonest humoral immunodeficiency, with a prevalence in Europeans of roughly 1:600.⁹¹ IgA deficiency is frequently asymptomatic and may be underreported. First identified by Buckley, it can be associated with elevation of serum IgE (range 3–3800 IU/mL).⁹² Diagnosis can only be made after 4th year of life and is defined by undetectable serum IgA levels (<0.07 g/L), normal serum IgG and IgM on at least

TABLE 3 Common autoimmune complications of IPEX, ALPS, DOCK8 and WASP deficiency

Disease	Prevalence
IPEX ⁶⁷	>90%
Autoimmune enteropathy	92%
Type 1 diabetes	49%
Autoimmune cytopenia	31%
Autoimmune thyroiditis	20%
Autoimmune hepatitis	6%
Others: including adrenal insufficiency, pemphigoid, psoriasis, alopecia, nephritis, arthritis	
ALPS ¹⁰⁴	61%
Autoimmune haemolytic anaemia	52%
Autoimmune thrombocytopenia	26%
Autoimmune neutropenia	8%
Vasculitis	4%
Autoimmune hepatitis	3%
Autoimmune nephritis	2%
Other: uveitis, pancreatitis	
WAS deficiency ⁷²	72%
Autoimmune haemolytic anaemia	36%
Autoimmune thrombocytopenia	33%
Autoimmune neutropenia	25%
Skin vasculitis	22%
Intestinal bowel disease	9%
Cerebral vasculitis	7%
Nephritis	4%
DOCK8 deficiency ⁴⁶	13%
Vasculitis	6%
Autoimmune haemolytic anaemia	3.7%
Autoimmune nephritis	0.7%
Others: Systemic lupus erythematosus, arthritis, autoimmune thyroiditis	4.4%

two determinations, normal IgG antibody response to vaccinations, and exclusion of secondary causes of hypogammaglobulinaemia and T-cell defects.⁹³ Up to 50% of sIgAD patients are recognized after an allergologic evaluation.⁹⁴ The most common allergic features are conjunctivitis, rhinitis, urticaria, eczema, food allergy and asthma.^{95,96} Patients with IgA deficiency may also present severe anaphylaxis when receiving IgA-containing blood products, possibly due to anti-IgA IgG or IgE antibodies.⁹⁷

7 | DIAGNOSTIC AND THERAPEUTIC OUTLOOKS

The therapeutic approach for many HIES-associated PID following diagnosis is much brighter, reflecting initiation of appropriate antimicrobial therapies, IGRT and consideration of HSCT. Early diagnosis

remains challenging as current diagnostic scoring systems, such as the NIH Score,² are reliant on emergence of sufficient immunological, infective and anatomical features. This signature may not emerge until irreversible damage has occurred. Judicious access to “clinical exomes” promises earlier and clinically impactful diagnosis,⁹⁸ and we highlight 5 clinical settings to trigger consideration of further investigation or referral. The monogenetic PID disorders continue to reveal molecular mechanisms underpinning our understanding of tolerance and immunity. Targeted therapeutic strategies are in development for Comel-Netherton syndrome, including protein replacement, tissue kallikrein inhibitors or using of autologous grafts of genetically corrected patient keratinocytes.⁹⁹ If successful, these promise to reveal whether restoration of barrier function can prevent development of the associated immunodeficiency. Whilst the role of barrier compromise in environmental allergen sensitization is well established, we are now recognizing the additional importance of the microbiota's ability to drive autoimmunity. In murine models of Omenn's syndrome, marked dysbiosis and translocation of gut commensals across the mucosal lining is associated with local inflammation, and systemic autoimmunity. Treatment with oral broad-spectrum antibiotics normalized serum hyper-IgE and ameliorated systemic autoimmunity.¹⁰⁰ Confirmation in human states are required; however, the implications are manifold. The interaction between the microbiota, barrier and mucosal immune system likely represents a modifiable factor contributing to the enteropathy seen in other PIDs associated with immune dysregulation and enteropathy, but potentially also the extreme rise in IgE described with graft-vs-host disease following HSCT.¹⁰¹ Normalization of the microbiota from the skewed populations observed in many HIES-PID may be an important means to optimize therapies and might explain the decline of IgE levels observed in some adults with STAT3-HIES.³ Restoration of epithelial defence is an attractive avenue. Chaperone modulators can ameliorate certain genotypes of cystic fibrosis, and this approach appears suitable for STAT3-HIES.¹⁰² This could be an important adjunct to HSCT, given the wide range of extra-haematological manifestations. Translation of current therapies such as dupilumab, a monoclonal anti-IL-4R α antibody, offers “off the shelf” options. Meanwhile, the potential for a dietary intervention guided by detailed characterization of molecular pathways revealed by CARD11 hints at wider implications for atopy sufferers. International collaborative efforts to standardize reporting, such as the USIDNET and ESID registry, are therefore vital to further characterize the true phenotypes of the expanding range of conditions and long-term outcomes of these emerging therapeutic options. Together this will help raise awareness and improve treatment for not only monogenic PID and may inform molecularly guided treatments for a much wider range of conditions.

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ORCID

Mark J. Ponsford  <http://orcid.org/0000-0002-0236-1059>

Tomas Milota  <http://orcid.org/0000-0003-2105-3462>

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