Primary Immune Deficiency

WE CAN DO MORE TO IDENTIFY PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

Sylvia van den Berg[1,2] | MBChB, MMed Clin Path, FC Path (Clin) DTM&H
Cathy van Rooyen[1,2] | MBChB, MMed Path, FRIC PATH
Robin J Green | PhD, DSc

Ampath Laboratories, Pretoria, South Africa

Department of Paediatrics and Child Health, Steve Biko Academic Hospital, University of Pretoria

Email | vandenbergs@ampath.co.za

Primary immunodeficiencies (PIDs) remain largely undiagnosed and underreported in South Africa.[1] PIDs are inherited, non-communicable disorders that involve a defect in one or more components of the immune system. Immunodeficiencies comprise more than 250 heterogenous disorders that cause either an absent, defective or weakened function of the immune system.[2] These disorders are mostly associated with recurrent infections that can present very early in childhood, but depending on the defect, also in later childhood and even in adulthood.

In early childhood, the immune system encounters antigens for the first time, mounting immune responses and acquiring memory. Young children mix with other family members and other children and are therefore exposed to many pathogens, making them vulnerable to infections. Recurrent infections are therefore quite common.[3,4] The delay in early PID diagnosis could be explained by a perception that recurrent infections are a normal part of childhood development.

The diagnosis of PIDs is therefore not always easy, especially among the many sick children seen in daily practice by general practitioners and paediatricians. These children often present with very common and non-specific complaints. It remains challenging to decide when to treat symptomatically and when to start investigating a patient for PID. Furthermore, a decision should be made about appropriate, cost-effective laboratory testing, correct

TABLE I: A SELECT GROUP OF THE MORE COMMON IMMUNODEFICIENCIES TAILORED FOR THE SOUTH AFRICAN PRACTITIONER – CONSTRUCTED WITH REFERENCE TO GEHA ET AL[5] AND AL-HERZ W, BOUSFIHA A, CASANOVA J ET AL[17]

PRIMARY IMMUNODEFICIENCIES	CLINICAL FEATURES
ANTIBODY DEFICIENCIES	**MUCOPURULENT SINOPULMONARY INFECTIONS**
• XLA • CVID • Specific antibody deficiency • Transient hypogammaglobulinaemia of infancy	
Combined T-/B-cell deficiencies • SCID • Omenn's Syndrome/Leaky SCID • Hyper-IgM Syndrome	Bacterial, fungal, viral infections, protozoal infections with/without failure to thrive and diarrhoea
NEUTROPHIL FUNCTIONAL DEFICIENCY	
• CGD	Abscesses and infections of parenchymal organs and lymph nodes
COMPLEMENT FUNCTIONAL DEFICIENCIES	
• Terminal complement pathway deficiency (most common)	Terminal complement deficiency with risk of meningococcal disease
IMMUNODEFICIENCY SYNDROMES	
• Wiskott Aldrich Syndrome	Bacterial and viral infections; thrombocytopaenia with small platelets; eczema; lymphoma/autoimmunity
• Ataxia Telangiectasia	Progressive ataxia/telangiectasis/immune deficiency
• Di George Syndome	Mostly mild/no immunodeficiency May present with incomplete T-cell defects with varying levels of CD4 cells Occasionally complete Di George: SCID-like presentation
• Hyper-IgE syndrome	AD form: Boils/pneumatocoeles/eczema-like skin rash/abnormal facies/failure to lose primary teeth AR form: severe and recurrent herpes viral infection. Persistent/recurrent molluscum contagiosum

CVID: common variable immunodeficiency; SCID: severe combined immunodeficiency. SLE: Systemic lupus erythematosus. AD: Autosomal Dominant. AR: Autosomal Recessive. MBL: Mannan Binding Lectin. CGD: Chronic granulomatous disease. XLA: X-linked agammaglobulinemia

TABLE II: FINDINGS SUGGESTIVE OF IMMUNODEFICIENCY

Persistent lymphopaenia (<1.5 × 10^9/ℓ in older children and <2.5 × 10^9/ℓ in younger children)
Unexplained, excessive frequency and/or severity of infection • Eight ear infections, two sinus infections per year (especially with mucopurulent discharge) • Two episodes of pneumonia within one year or chronic suppurative chest infection • Rare or unusual complications, for example, complicated varicella
Dependence on or refractory to antibiotic treatment • Need for intravenous antibiotics to clear infection • Two or more months on antibiotics to little effect
Infectious syndromes • More than one organ involved • Recurrent deep skin or organ abscesses • Two or more deep-seated infections (eg sepsis, meningitis, pneumonia)
Organisms • Less virulent or opportunistic causative agent • Persistent oral thrush or cutaneous candidiasis (especially in children older than four months) • *Neisseria meningitides* meningitis. In certain settings such as the Western Cape, it may be appropriate to screen with total haemolytic complement
Constitutional symptoms • Failure to thrive • Persistent, extensive, atypical dermatitis or erythroderma • Chronic diarrhoea
Clinical examination • Lymph nodes and tonsils may be absent in severe PID • Evidence of chronic ear infection • Evidence of bronchiectasis
Family history • PID • Unexplained sudden death in infancy • Consanguinity
Age and gender • SCID presents in early infancy • Profound antibody deficiency usually presents in first year of life • Severe immunodeficiencies more commonly affect boys
Unexplained fever or autoimmunity
Additional features in infants include: • Delayed umbilical separation (>30 days) • Congenital heart defects • Hypocalcaemia • Absent thymic shadow on CXR

timing of these tests, proper interpretation thereof and what constitutes sufficient testing.[3,5]

A recent survey in the United States assessed management of PIDs by family practice physicians. Only a few family practice physicians were aware of professional guidelines for diagnosis and management of PID (4 vs 79% of subspecialist immunologists).[6] It is commonly assumed that PIDs are rare childhood disorders, but common variable immunodeficiency (CVID) has an estimated prevalence of 1 : 10 000–1 : 50 000 and is mostly an adult disorder. Diagnosis of combined immunodeficiencies may even be delayed into adulthood.[7] A population-based, newborn screening programme in the United States reported an overall incidence of severe combined immunodeficiency (SCID) at 1 : 33 000 and T-cell lymphopaenia of 1 : 6 600.[8]

The question therefore arises: What more can we do to recognise these patients timeously in order to treat them quickly and sufficiently and to prevent complications?

TABLE III: FINDINGS AGAINST PID

- Recurrent infection of one organ only
- Another explanation or known exposure that predisposes to infection
- Failure to find a causative pathogen despite repeat testing (consider non-infective cause of symptoms)

BE AWARE THAT THEY EXIST

The field of PID has evolved and an increasing number of PIDs are now recognised.[9,10,11] Most immunodeficiencies are caused by an antibody (B-cell) deficiency or a combined antibody plus cellular (T-cell) deficiency. Isolated T-cell deficiencies, complement and phagocytic cell deficiencies are much less common.[12]

The more common and/or serious PIDs observed in clinical practice are summarised in Table I.[13,14]

PIDs can present to a variety of clinicians with various symptoms and increased awareness should therefore be taught on a pregraduate and postgraduate level.

KNOW THE RED FLAG SIGNS

Pattern recognition of a constellation of clinical findings over a period of time or certain immediate clues should be used to alert clinicians to the possibility of an underlying immune deficiency. A limited set of easily available laboratory investigations can then be used to further guide in the initial workup.[15]

A constellation of red flag signs, in isolation or in combination, should prompt one to look for an immunodeficiency (Tables II and III).[13,16]

Any one of the following is regarded as the most suggestive of an underlying immune deficiency: a family history of a PID including history of an early infant death due to an infection, sepsis in children requiring intravenous antibiotics and failure to thrive.[16] In the South African context, bacillus Calmette-Guérin (BCG) dissemination, paralytic poliomyelitis, recurrent meningococcal infections, PJP (*Pneumocystis jirovecii* Pneumonia) in HIV-negative patients and infections with atypical mycobacteria should be additional highlighted warning signs.[1] An acronym to assist with the diagnosis of PID was endorsed by the Primary Immunodeficiency Network of South Africa (PINSA), namely, SPUR: Severe, Persistent, Unusual and Recurrent (SPUR) infections.[5]

Secondary causes of immunodeficiencies should always be excluded and include HIV/AIDS, malignancies, infections, immunosuppressive medication, diabetes mellitus, dialysis and ureamia, protein-losing conditions, liver disease, malnutrition, trauma and burns, ionising and ultraviolet radiation, toxic chemicals, pregnancy, old age and severe stress.

TABLE IV: IMMUNODEFICIENCIES AND ASSOCIATED PATHOGENS

PATHOGENS AND INFECTIONS	ASSOCIATED PID
Recurrent sinopulmonary infections with encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Moraxella catarrhalis)*	B-cell disorders
Recurrent pneumococcal infections	Humoral, complement or innate deficiency
P neumocystic jirovecii pneumonia	T-cell deficiencies including SCID, CD40 ligand deficiency
Pseudomonas aeruginosa	Severe phagocytic, humoral or T-cell deficiencies, also cystic fibrosis, neutropaenia and soft tissue injury
Enteroviral meningo-encephalitis	Agammablobulinaemia or severe CVID
Recurrent infections with *S aureus*, Coagulase Negative Staphylococci, *Serratia marcescens*, *Chromobacterium violaceum* or *Aspergillus spp.*	Phagocyte dysfunction
Recurrent Staphylococcal skin infections, abscesses, lung cysts or pneumonia	Hyper-IgE syndrome
Recurrent herpes viral infections, including HSV, CMV and EBV	NK cell deficiencies and combined T-cell defects including DOCK 8 deficiency
Infections with live vaccines (including BCG, oral polio vaccine, measles, rota virus, varicella)	Severe primary immunodeficiencies, including SCID and XLA
Prolonged or recurrent Candida infections involving the mucous membranes	T-cell immunodeficiency, immune dysregulation syndromes including APECED
Recurrent invasive Neisserial infections	Late component complement deficiency
Systemic or deep infections with nontuberculous mycobacteria	Interferon gamma or interleukin receptor deficiency
Recurrent molluscum contagiosum and/or persistent/extensive/recurrent warts	T-cell defect, innate immune defect or combined defect called WHIM

BCG: BacilleCalmette Guerin; DOCK 8: Dedicator of cytokinesis 8; APECED: Autoimmune Polyendocrinopathy-candidiasis-ectodermal dystrophy; CVID: Common variable Immune Deficiency; XLA: X-linked agammaglobulinemia; SCID: Severe Combined Immune Deficiency;HSV: Herpes simplex virus; CMV: Cytomegalovirus infection; EBV: Epstein-Barr virus; BCG: BacilleCalmette-Guerin; WHIM: Warts, hypogammaglobulinaemia, infection, myelokathexis syndrome

KNOW THE SENTINEL ORGANISMS

The type of organism can also provide clues as to the nature of the underlying immune deficiency (Table IV).[17] Being well-versed in local infectious diseases is, therefore, paramount for PID recognition, making well-trained local paediatricians crucial for early PID diagnosis.[18] Infections with certain organisms should set off the alarm bells. These include infections with organisms that we find in the context of HIV infection. A negative HIV test with/without a low CD4 count with an infection of an unusual organism therefore does not equate to laboratory error or an insignificant finding – think PID.

Antibody deficiency disorders often present with encapsulated invasive bacteria and patients with low IgA levels (ie IgA deficiency or CVID) may often have protracted diarrhoea caused by the parasite *Giardia lamblia*. Patients with agammaglobulinaemia are especially susceptible to infections with enteroviruses, which may lead to chronic meningo-encephalitis. They may also suffer from severe infections with intracellular bacteria, including *Mycoplasma pneumoniae* and *Ureaplasma urealyticum* arthritis.

Recurrent viral, fungal, mycobacterial or protozoal infections may suggest a T-cell defect. The opportunistic pathogens that one usually finds in the context of HIV/AIDS, namely, *Pneumocystis jirovecii* and *Mycobacterium avium intracellulare,* are clues that an underlying T-cell defect may exist.

Lymphadentis and recurrent abscesses caused by low-virulence, gram-negative bacteria including *Escherichia coli*, *Burkholderia cepacia*, *Serratia spp* or *Klebsiella spp* and recurrent *Staphylococcus aureus* infection or invasive Aspergillosis may indicate abnormalities in granulocytes such as chronic granulomatous disease.[17]

In addition to being of help in establishing the diagnosis, PID patients are also more susceptible to develop these infections once diagnosed. It is therefore important to have a high index of suspicion and to do appropriate cultures and PCRs in consultation with a microbiologist to ensure adequate sampling and testing procedures are followed, in order to identify and treat infections appropriately.

KNOW WHICH DIAGNOSTIC TESTS TO ORDER

A stepwise approach to the diagnosis of PIDs was proposed and developed by the Jeffrey Modell Foundation (JMF) and modified for use in South Africa (Table V).[18,19] Most of the laboratory testing is widely available and the more specialised tests can be offered by some private laboratories in consultation with the immunology pathologists. Many of these specialised tests are functional assays and should ideally be performed at a stage when the patient is infection-free. Antibody levels should be measured before immunoglobulin replacement therapy has been instituted. A tiered approach should be followed and be directed towards the most likely immune deficiency as directed by clinical history and examination.[19]

TABLE V: A STEPWISE APPROACH TO THE LABORATORY DIAGNOSIS OF PID

	TEST	ASSOCIATION
	EXCLUDE HIV	
First-line investigations	Assessment for atopy	As indicated on history
	Full blood count • Differential count for neutrophil and lymphocyte numbers • Platelet count and morphology	Lymphopaenia is an important indicator of possible SCID Small platelets seen in Wiskott-Aldrich syndrome
	Serum (IgG, M, A and E),	IgE should be tested in patients who may be at risk of hyper-IgE syndrome
	CF screening	Suspected on history and clinical examination
	Investigation for active TB	
Second-line investigations	Specific antibody response • Targeted to polysaccharide-specific antigens (*S pneumoniae*) and protein antigens (tetanus, diphtheria and *H influenzae*)	**Indicated with recurrent bacterial infections, even in the presence of normal immunoglobulins**. Patients have to be off immunoglobulin replacement therapy for six months. If these antibody levels are decreased, the patient should be revaccinated and antibody responses should be repeated four weeks after vaccine boosting to determine an appropriate increase in specific antibody responses. Please note that an unconjugated pneumococcal vaccine, for exmaple Pneumovax® should be given to determine an appropriate polysaccharide antigen response.
	Lymphocyte subsets • B-cell numbers (CD19) cells should also be measured.	Absent in XLA-linked agammaglobulinaemia when all immunoglobulin isotypes are severely reduced
	T-cell numbers (CD3). T-helper (CD4) and T-suppressor (CD8)	Reduced in T-cell defects, combined immunodeficiencies and occasionally CVID
	Natural killer cells (CD16 and CD56)	Isolated NK-cell deficiencies may be associated with recurrent herpes virus infections
	Neutrophil function • Neutrophil oxidative burst	CGD
Third-line investigations	Lymphocyte proliferation studies • Response to mitogens, for example PHA, PMA, PMA +ionomycin, anti-CD3, anti-CD3+IL2 or to recall antigens, for example Candida, tetanus, varicella	T-cell deficiencies including SCID, Chronic mucocutaneous candidiasis. Specialist input valuable as to when to request a certain mitogen/s or recall antigen/s
	Neutrophil antibodies	Auto-immune and alloimmune neutropaenia
	Lymphocyte maturation panel: naïve and memory T-cells	Diagnosis of SCID and combined T-cell defects
	Recent thymic emigrants (T-cells)	Very low in SCID Can be used to monitor bone marrow regeneration post transplant
	Memory B-cells	Memory B cells categorise subsets of CVID patients
	Alpha/beta, gamma/delta T-cell receptor type	Abnormal in leaky SCID, hypomorphic SCID, T-cell defects with oligoclonality
	TRECs and KRECs (can also be considered as a first-line investigation – see text)	Used for neonatal screening for SCID and XLA on blood monospots – useful to do prior to giving live vaccines at birth
	Total haemolytic complement • Classic complement pathway • Alternative complement pathway	Complement deficiencies
Fourth-line investigations	• Genetic studies	Maybe appropriate as third-line test in some patients
	• T-regulatory cells	Fox P3 deficiency: decreased in IPEX syndrome
	• Th-17 cells	Decreased in HIGE syndrome
	• Surface markers for X-linked SCID: CD132, IL-7Rα	Diagnosis of X-linked SCID
	• HLADR	Absent in MHCII deficient SCID
	• BTK (diagnosis of XLA)	Absent in most boys with XLA
	• CD40L	Absent in most boys with X-linked HIGM
	• CD40	Absent in some patients with HIGM
	• MBL	Low MBL levels may predispose patients to upper respiratory tract infections and they may have a higher risk for severe menigococcal or pneumococcal infections
	• NK-cell cytotoxicity assay	Markedly reduced in FHL. Abnormal in primary NK-cell defects
	• Neutrophil studies for leukocyte adhesion, chemotaxis and phagocytosis	
	• CD11 and CD18	Leukocyte adhesion defects

Adapted from M Esser and B Eley[18] and MS Suchard, S Buldeo, S van den Berg and C van Rooyen[20,21]

TREC: T-cell receptor excision circles; KREC: Kappa receptor excision circles; SCID: severe combined immunodeficiency; BTK: Brutons tyrosine kinase; CGD: Chronic granulomatous disease; XLA: X-linked agammaglobulinaemia; PMA: PhorbolMyristate Acetate; CD3 = Cluster of differentiation 3; IL2 = Interleukin 2; CVID = Common Variable Immune Deficiency; CGD = Chronic Granulomatous Disease; MBL: Mannan Binding Lectin; CF: Cystic fibrosis; PHA: phytohaemagglutinin; HLADR: Human Leukocyte Antigen - antigen D Related; MHCII: Major histocompatibility complexclassII; HIGM: Hyper IGM; HIGE: Hyper IGE; FHL: Familial haemophagocytic lymphohistiocytosis

TABLE VI: INCIDENTAL LABORATORY FINDINGS THAT MAY BE ASSOCIATED WITH A PID

LABORATORY FINDING	CLINICAL IMPLICATION
BIOCHEMISTRY	
Low immunoglobulins	Humoral and combined immunodeficiencies. Secondary immunodeficiencies
High immunoglobulins	May implicate HIV, autoimmune disorders, chronic inflammation and granulomatous disease
Low IgA during Coeliac disease serology	Specific IgA deficiency has a higher prevalence in patients with coeliac disease
High IgE (10 × upper limit for age)	Hyper-IgE syndrome, WAS, IPEX, DOCK 8 deficiency, etc, although the majority remain secondary to atopic disease
Low IgE (<2 IU)	May represent antibody deficiency in 7% of patients
Serum calculated globulin fraction (total protein – albumin)	Antibody deficiencies can reduce the globulin fraction – usually <19g/ℓ
Serum protein electrophoresis	Hypogammaglobulinaemia without a monoclonal protein may indicate a possible antibody deficiency
HAEMATOLOGY	
Lymphopaenia	Persistent unexplained lymphopaenia may be a key clue suggesting PID
Persistently absent or very low monocyte count	GATA-2 deficiency that predispose to human papilloma virus and/or atypical mycobacterial infection and high risk of myelodysplasia and acute myeloid leukaemia
Low platelet count	ITP may be a presenting feature of immunodeficiency. Similarly, also autoimmune haemolytic anaemia and autoimmune neutropaenia. ITP can be present in up to 6% of patients with CVID[23]
Low platelet volume	This is strongly suggestive of the rare Wiskott-Aldrich syndrome
CYTOGENETIC TESTING	
A failed cytogenetic test (ie lymphocytes fail to proliferate after mitogen stimulation)	Prompt consideration of SCID
MICROBIOLOGY/VIROLOGY TESTING	
Failed vaccine responses	Clinical episode of measles in a patient fully vaccinated, failure to respond to Hepatitis B vaccination (may occur in 10–15% of the normal population) and rubella vaccination
Unusual or recurrent positive cultures Recurrent *S pneumoniae* and *H influenzae* Gastrointestinal infection with *G lamblia* and *Campylobacter jejuni* Recurrent or severe Candida infections *P jirovecii* pneumonia Recurrent, unexpected or severe viral infections, for example CMV, HPV	See Table IV for immunodeficiencies and associated pathogens
HISTOPATHOLOGY	
Unexplained granulomata	CVID and chronic granulomatous disease should be considered
Absent germinal centres on lymph node biopsy	This should prompt measurement of lymphocyte subsets and immunoglobulins
Villous shortening	May be associated with *G lamblia* infection which is a common infection in antibody deficiencies
Absence of plasma cells in biopsies, for example GIT	May be seen in humoral immunodeficiencies

WAS: Wiskott-Aldrich syndrome; IPEX: Immune dysregulation, polyendocrinopathy, enteropathy and X-linked syndrome, DOCK 8: Dedicator of cytokinesis 8; ITP:Immune thrombocytopenic purpura; CVID: Common variable immunodeficiency;SCID: Severe combined immunodeficiency; GIT: Gastro-intestinal tract

The first- and second-line investigations will detect the majority of common PIDs and will warrant sufficient investigations in the majority of settings. Functional testing may be challenging for peripheral centres that are not close to the referring laboratories, as sample stability during transit may be problematic. Genetic testing may be considered to bypass logistic challenges inherent to functional testing.

CONSIDER IMMUNODEFICIENCY WHEN INTERPRETING ABNORMAL PATHOLOGY TESTS UNDERTAKEN FOR OTHER REASONS

Abnormal laboratory results may indicate a possible immunodeficiency as demonstrated in Table VI.[22] This may prompt additional clinical and laboratory investigations to exclude or confirm a suspected immunodeficiency.

AIM TO IDENTIFY PATIENTS PRIOR TO THE ONSET OF CLINCIAL SYMPTOMS

Newborn screening for severe PIDs involving the cellular and humoral immune system allows early detection and treatment, potentially saving the lives of babies affected by the disease. PCR assays to detect T-cell receptor excision circles (TRECs) and Kappa-deleting receptor excision circles (KRECs) in newborn blood have been available in South Africa since 2013. These assays

have been developed to detect diseases hallmarked by the absence of T- or B-lymphocytes, classically seen in severe combined immunodeficiency (SCID) and X-linked agammaglobulinaemia (XLA)/Bruton's disease. Babies with SCID appear healthy at birth, but without early treatment, most of these babies die before the age of one year. Research indicates that infants with SCID who receive haematopoietic stem-cell transplants in the first 3.5 months of life have a better chance of survival as compared with infants receiving this treatment after 3.5 months (95% vs 76%). It is crucial to make this diagnosis as early as possible, before the patients receive live vaccines or present with infections. This is because live vaccines and infections can be fatal, as well as greatly diminish the success rate of the bone-marrow transplant.[24]

Patients with XLA usually present later in life due to protective maternal antibodies, but are at great risk to develop infections after receiving live vaccines such as oral polio, which can lead to fatal infections. These patients are also at risk of severe infections, especially pulmonary infections. Pulmonary complications are the most common cause of mortality and morbidity in these patients. Early identification can prevent the administration of live vaccines and aid in early initiation of immunoglobulin replacement therapy, which can prevent pulmonary and other infectious complications.[25,26]

Newborn screeing for SCID is available on request in the private healthcare setting. Routine newborn SCID screening using existing methodology may be costly to implement in the public healthcare setting, but high-volume testing using alternate methods can drive costs down substantially and make newborn screening for SCID a cost-effective option.

JMF has developed a working algorithm or 'decision tree' for the implementation of newborn screening programmes for SCID. This algorithm has been validated by peer-reviewed scientific literature, and is intended for use by public health departments and health ministries in countries throughout the world. This decision tool allows for local or regional data to be applied to measure the threshold and economic impact of implementing newborn screening for SCID and T-cell lymphopaenia. This can be applied in the South African healthcare setting to evaluate the cost-efficacy of newborn screening for SCID.[8]

AIM TO MAKE A DEFINITIVE DIAGNOSIS

More than 250 genetic defects may result in PID.[2,9] Genetic testing can establish or confirm a suspected diagnosis and may predict future disease risk, inform reproductive decision-making and guide in selecting the most appropriated therapies. One should, however, be aware of testing limitations and patients and their families should be properly informed and counselled.[27]

TABLE VII: IMMUNODEFICIENCIES COVERED BY A PID GENETIC PANEL AVAILABLE IN SOUTH AFRICA

• SCID
• Hyper-IgM syndrome
• Hyper-IgE syndrome
• Immune dysregulation
• CVID
• Lymphoproliferative syndromes, including autoimmune lympho-proliferative syndrome
• CGD
• MHC Class I and MHC Class II deficiencies
• Anhidrotic ectodermal dysplasia with immunodeficiency
• Autoimmunity with lymphoproliferation
• Antibody deficiencies
• T-regulatory cell defects
• FHL, including FHL with hypopigmentation
• Chemokine signalling defects
• Innate immunity defects
• Complement deficiencies
• Isotype deficiencies
• Thymic defects with congential abnormalities

SCID: Severe combined immunodeficiency; CVID: Common variable immunodeficiency; CGD: Chronic granulomatous disease; MHC I and II: Major histocompatibility complex class I and II; FHL: Familial haemophagocytic lymphohistiocytosis

Genetic testing available in South Africa includes a private commercial genetic panel (Table VII), Whole Exome sequencing (WES) at the University of Stellenbosch and private laboratories, PID gene panels from international centres, for example the GOSH panel from Oxford, and various research collaborations involving WES.

If a PID gene panel is negative, further steps of exome and genome sequencing can be undertaken.[1]

TRAINING OF PRE- AND POSTGRADUATE MEDICAL STUDENTS IN IMMUNOLOGY

Appropriate training of pre- and postgraduate medical students in Immunology is essential to ensure adequate diagnosis and management of patients with PID. Clinical Immunology is not offered as a postgraduate training programme in South Africa, although Clinical Immunology is recognised as a postgraduate medical qualification in many countries including United States, the United Kingdom and other African counties. The need for pre-and postgraduate training in Clinical Immunology in South Africa needs to be addressed to facilitate improved diagnosis and care of PID patients.

ACCESS TO CARE

If a clinician suspects a PID on clinical grounds or the basis of an abnormal laboratory test, the available referral pathways for clinicians include Steve Biko/University of Pretoria, Stellenbosch University and University of Cape Town specialist PID centres. PINSA is a valuable resource

of information for patients and clinicians and can advise on routes of access to care.

REPORTING PATIENTS WITH PID ON THE SA PID REGISTRY

The South African PID registry is part of an ethically approved confidential research project to estimate the prevalence of PID in South Africa. This registry helps create awareness of PIDs in South Africa and information in this registry plays an important role in research and lobbying. The registry provides objective evidence needed to change policies, inform medical aids and improve patient outcomes through data-sharing.[1] Lack of access to care is one of the main reasons why PID remains largely under-diagnosed and underreported in South Africa.

CONCLUSION

Most children with recurrent infections have a normal immune system, but it is important to recognise the child with an immunodeficiency in order to manage and treat timeously and appropriately. Humoral immunodeficiencies often present in adult patients and PIDs are therefore not only paediatric disorders. It cannot be overemphasised that a high index of suspicion should always be maintained for possible immunodeficiencies, as untreated immunodeficiencies are life-threatening. In this regard, MA Slatter and AR Gennery have stated:

> '... the question to be asked in a patient presenting with recurrent infections is not "Who should be investigated for primary immunodeficiency ?" but "What are the reasons for not investigating further?"'[28]

As immunodeficiencies may be complex and difficult to diagnose, it is recommended that advice be sought from clinical immunologists, paediatricians, physicians, ENT surgeons, pulmonologists and the immunology laboratory in the workup of difficult patients.

DECLARATION OF CONFLICT OF INTEREST

Dr S van den Berg and Dr C van Rooyen are employed at Ampath Laboratories.

This article has been peer reviewed.

REFERENCES

1. Esser MM, Potter P, Nortje R. Meeting the needs of primary immunodeficiency patients in South Africa – some findings from the South African Registry. Curr Allergy Clin Immunol J 2016;29(1):56–61.
2. Al-Herz W, Bousfiha A, Casanova JL, Chapel H, et al. Primary immunodeficiency diseases: An update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Fron Immunol 2011;2:1–26.
3. Van Niekerk A, Esser MM. A diagnostic approach to recurrent respiratory tract infections in childhood: Could it be primary immunodeficiency? Curr Allergy Clin Immunol J 2015;28(4):308–312.
4. Slatter MA, Gennery AR. Clinical immunology review series: An approach to the patient with recurrent infections in childhood. Clin Exp Immunol 2008;152:389–396.
5. Bush A. Recurrent respiratory infections. Pediatr Clin N Am 2009;56:67–100.
6. Orange JS, Seeborg FO, Boyle M, Scalchunes C, et al. Family physician perspectives on primary immunodeficiency diseases. Front Med (Lausanne) 2016;3(12).
7. Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency – an update. Arthritis Res Ther 2012;14:223.
8. Modell V, Knaus M, Modell F. An analysis and decision tool to measure cost benefit of newborn screening for severe combined immunodeficiency (SCID) and related T-cell lymphopenia. Immunol Res 2014;60(1):145–152.
9. Bousfiha AA, Jeddane L, Ailal F, Al-Herz W, et al. A phenotypic approach for IUISPID classification and diagnosis: Guidelines for clinicians at the bedside. J Clin Immunol 2013;33:1078–1087.
10. Bousfiha AA, Jeddane L, Ailal F, Benhasaien I, et al. Primary immunodeficiency diseases worldwide: More common than generally thought. J Clin Immunol 2013;33:1–7.
11. Parvaneh N, Casanova JL, Notarangelo LD, Conley ME. Primary immunodeficiencies: A rapidly evolving story. J Allergy ClinImmunol. 2012;131:314–323.
12. Modell V, Knaus M, Modell F, Roifman C, et al. Global overview of primary immunodefiencies: A report from Jeffrey Modell Centers worldwide focused on diagnosis, treatment, and discovery. Immunol Res 2014;60(1):132–144.
13. Gray PE, Namasivayam M, Ziegler J. Recurrent infection in children: When and how to investigate for primary immunodeficiency? J Paediatr Child Health 2012;48(3):202–209.
14. Al-Herz W, Bousfiha A, Casanova J, Chatila T, et al. Primary immunodeficiency diseases: An update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Front Immunol 2011;2(54)1–26.
15. De Vries E, Driessen G. Primary immunodeficiencies in children: A diagnostic challenge. Eur J Pediatr 2011;170:169–177.
16. Primary Immunodeficiency Association. Publications: 10 warning signs of a primary immunodeficiency. Available at: www.pia.org.uk/publications/10_signs_of_pia/10_signs_01.htm (accessed 14 March 2011).
17. Bollow M. Approach to the Patient with recurrent infections. Clinic Rev Allergy Immunol 2008; 34:129–140.
18. Savides C, Shaker M. More than just infections: An update on primary immune deficiencies. Curr Opin Pediatr 2010;22:647–654.
19. Eley B, Esser M. Investigation and management of primary immunodeficiency in South African children. SAMJ 2014;104(11).
20. Suchard MS, Buldeo S, Van Rooyen C. Appropriate investigation for primary immunodeficiency in South Africa. Curr Allergy Clin Immunol J 2012;25(4)190–197.
21. Van den Berg S, van Rooyen C. When to suspect primary immune deficiency in children. Infectious diseases update. 2015;4(4):7–11.
22. Bright PD, Rooney N, Virgo PF, Lock RJ, et al. Laboratory clues to immunodeficiency; missed chances for early diagnosis? J Clin Pathol 2015;68:1–5.
23. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol1999;92:34–48.
24. Van der Spek J, Groenwold RH, Van der Burg M, Van Montfrans JM. TREC based newborn screening for severe combined immunodeficiency disease: A systematic review. J Clin Immunol 2015;35(4):416–430.
25. Lindegren ML, Kobrynski L, Rasmussen SA, Moore CA, et al. Applying public health strategies to primary immunodeficiency diseases. MMWR recommendations and reports. 2004;53(RR01);1–29.
26. Barbaro M, Ohlsson A, Borte S, Jonsson S, et al. Newborn screening for severe primary immunodeficiency diseases in Sweden – a 2-year pilot TEC and KREC screening study. J Clin Immunol 2017;37(1):51–60.
27. Morra M, Geigenmuller U, RainvilleIR, Curtis J, et al. Genetic diagnosis of primary immune deficiencies. Immunol Allergy Clin N Am 2008;28:387–412.
28. Slatter MA, Gennery AR. Clinical Immunology Review Series: An approach to the patient with recurrent infections in childhood. Clin Exp Immunol 2008;152:389–396.

14. Graveling RA, Pilkington A, George JPK, Butler MP, et al. A review of multiple chemical sensitivity. Occup Environ Med 1999;56:73–85.
15. Bornschein S, Hausteiner C, Zilker T, Forstl H. Psychiatric and somatic disorders and multiple chemical sensitivity (MCS) in 264 'environmental patients'. Psychol Med 2002;32(7):1387–1394.
16. Occupational Health and Safety Amendment Act 181 of 1993. http:www.labour.gov.za

RECOMMENDED FURTHER READING

1. Mulitple Chemical Sensitivity – the end of controversy. Martin_pall@wsu.edu 2016. www.laleva.cc/environment/mcs_en.html. This discusses Professor Pall's ongoing research into the role of nitric oxide on neural sensitisation.
2. Sparks PJ (editor). Multiple Chemical Sesitivity/Idiopathic Environmental Intolerance. Occupational Medicine: State of the Art Reviews 2000;15.
3. This is a 170-page publication which covers many aspects of MCS, including its aetiology, diagnosis and treatment.
4. Black DW, Temple S. Overview of idiopathic environmental intolerance (multiple chemical sensitivity) UpToDate 2015. <www.uptodate.com/contents/overview-of-idiopathic-environmental-intolerance-multiple-chemical-sensitivity>
5. Gibson PR, Elms AN, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. Environmental Health Perspectives 2003;111:1498–1504.

CPD QUESTIONNAIRE

Earn 3 CPD points after you have read the journal by completing the following questionnaire online on the ALLSA website at www.allergysa.org. To earn points you need to log in to the member section to access the questionnaire (contact ALLSA office if you do not know your user name and password). There is only one correct answer and you will have only two opportunities to submit the questionnaire, so please check answers carefully. A pass of 70% or higher is required to gain 3 points. Ethics CPD points are assigned to questions 1-10

PATIENT EMPOWERMENT: CREATING EFFECTIVE PARTNERSHIPS BETWEEN THE PATIENT AND THE HEALTHCARE DELIVERY CHAIN

1. *True or false:* Litigation by empowered patients against their health care providers is becoming less frequent.
2. *True or false:* Even very young children have the right to decide whether or not to accept or reject treatment.
3. *True or false:* Patient empowerment increases treatment compliance and disease morbidity.
4. *Choose the **incorrect** answer:*
   a. Patient empowerment is detrimental to their effective treatment by their doctor;
   b. The Information and Technology revolution has assisted in creating empowered patients;
   c. Self-help groups and common community networks have a valuable role to play in supporting those with chronic illnesses;
   d. Patients put as much value on information which they have sourced themselves as they do on their doctor's advice.

HEALTH PROFESSIONALISM AND ETHICS – IS THERE A DIFFERENCE?

5. *True or false:* The Ethics Institute of South Africa survey revealed that doctors feared the consequences to themselves if they reported medical misconduct by a colleague.
6. *True or false:* A profession is defined as a calling requiring specialised knowledge and long and intensive academic preparation.
7. *True or false:* One of the hallmarks of a profession is the right to self-regulation.
8. *True or false:* In medieval times guilds were established to protect the interests of skilled workers, and these were the forerunners of the professions.
9. *True or false:* Surgeons and apothecaries had university training in medieval times, and were therefore seen as professionals.
10. *True or false:* The Physician Charter, a product of a working group on medical professionalism, contained three fundamental principles and ten commitments required of professionals.

PROMOTING ACCESS TO SAFE MEDICINES FOR CHILDREN

11. *True or false:* The Convention on the Rights of the Child states that governments should ensure adequate health care provision for children.
12. *True or false:* The Essential Medicine List includes only medicine for infectious diseases in low- and middle income countries.
13. *True or false:* Off label medicine use in children is a criminal offence.
14. *Choose the **incorrect** answer:* Advocacy for better medicines for children includes the following:
    a. Encourage doctors to undertake clinical trials with paediatric patients for medicines commonly used off-label in children.
    b. Restrict paediatric clinical trials as it is exploitation of vulnerable individuals who cannot take care of themselves.