Chapter 31

PRIMARY IMMUNE DEFICIENCIES

Primary immune deficiencies (PIDs) are inherited, non-communicable disorders that involve a defect in one or more components of the immune system. Primary immune deficiencies are caused by a genetic defect, whereas secondary immune deficiencies occur when the immune system is compromised due to an environmental factor. Examples of secondary immune deficiencies include: the treatment of malignancies, HIV infection, protein-losing conditions, autoimmune disorders and lymphoproliferative disorders. More than 250 known heterogeneous disorders may cause primary immune deficiency. 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.

Primary immune deficiencies have an overall prevalence of one per 10 000 and one per 20 000 in Europe and the United States respectively. Recent epidemiologic surveys estimated that as many as six million people worldwide are living with a primary immune deficiency, with the majority being undiagnosed. PIDs remain largely undiagnosed and underreported in South Africa. It is estimated that the total number of PIDs in South Africa is between 2 850 and 45 723 cases, based on a mid-2013 population estimate of 52.98 million; however, only about 317 cases have been reported in South Africa. The question therefore arises: What more can we do to recognise and diagnose these patients earlier in order to treat them and to prevent complications and fatalities?

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 and recurrent infections. 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 simply treat and when to start investigating a patient for a possible PID. Early diagnosis and treatment of PIDs save lives, reduce and prevent complications and improve quality of life. However, PIDs are often not detected until after the patient has experienced repeated infections which may lead to significant morbidity and mortality. The time between onset of infections and the diagnosis of a PID may be as long as 12 years.

The child with ‘recurrent infections’ is a common scenario in clinical practice. ‘Recurrent infections’ may refer to infections that:

- are more frequent in number
- are unusually severe
- are unusually long lasting
- are associated with unusual complications
- fail to be resolved with standard therapy

The causes for recurrent infections are multiple and HIV-uninfected children can be grouped into four clinical categories:

- The 'normal' child – 50%
- The atopic child – 30%
- The chronically ill child –10%
- The child with a primary immune deficiency – 10%

THE 'NORMAL' CHILD (50%)

The average child has four to eight respiratory infections per year. Exposure to crèche or school-going siblings may increase this to 9–10 infections per year. Poor nutrition, overcrowding and passive smoking may also increase a child's predisposition to infection, including bacterial skin infections, respiratory tract and middle ear infections. Most of the respiratory infections in these children are viral in aetiology and children recover completely and appear healthy between infections. The physical examination and laboratory tests are normal and they have appropriate growth and development.

THE CHILD WITH ATOPIC DISEASE (30%)

Chronic allergic rhinitis may be mistaken for chronic or recurrent upper respiratory tract infections. Children with atopic disease usually have normal growth and development. Typical physical characteristics of atopy may be found on clinical examination, including allergic 'shiners' and a transverse nasal crease. These patients often develop coughing and wheezing following viral respiratory tract infections. Atopic patients respond poorly to antibiotics, but well to allergy and asthma medications. Be aware that immunodeficiencies and atopy may co-exist, including selective immunoglobulin A (IgA) deficiency, common variable immune deficiency (CVID), chronic granulomatous disease (CGD), and DiGeorge syndrome. Certain immunodeficiencies may also present with elevated IgE levels, including hyper IgE syndrome, Wiskott-Aldrich syndrome, Omenn syndrome, Dock 8 deficiency and IPEX syndrome.

THE CHILD WITH CHRONIC DISEASE (10%)

These children often have poor growth with failure to thrive and a sickly appearance. Diseases in this category include cystic fibrosis (CF), gastroesophageal reflux, congenital heart disease and chronic aspiration. There are usually other clinical findings and laboratory abnormalities indicative of the chronic disease.

THE CHILD WITH A PRIMARY IMMUNE DEFICIENCY (10%)

The patient with a PID suffers from recurrent infections that are persistent, unusual, recurrent or serious and may not respond to conventional oral antibiotics. Failure to thrive is especially observed in patients with more serious T-cell or neutrophil defects and a family history should never be ignored or underestimated. Infections are a key clinical feature, but patients may also present with autoimmunity, atopy or malignancies.

WHAT MORE CAN BE DONE TO IDENTIFY PATIENTS WITH PRIMARY IMMUNE DEFICIENCIES?

BE AWARE THAT PRIMARY IMMUNE DEFICIENCIES EXIST

The field of primary immune deficiencies has evolved and an increasing number of PIDs are now recognised. The more common and/or serious PIDs observed in clinical practice are summarised in the table on the next page.

THE MORE COMMON PRIMARY IMMUNE DEFICIENCIES

PRIMARY IMMUNE DEFICIENCY	CLINICAL FEATURES
ANTIBODY DEFICIENCIES	
• X-linked agammaglobulinemia (XLA) • Autosomal recessive agammaglobulinaemia • Common variable immune deficiency (CVID) • Specific antibody deficiency • Transient hypogammaglobulinaemia of infancy	Mucopurulent sinopulmonary infections
COMBINED T/B-CELL DEFICIENCIES	
• Severe combined immune deficiency (SCID) • Omenn syndrome • Hyper IgM syndrome	Bacterial, fungal, viral infections, protozoal infections with/without failure to thrive and diarrhoea
NEUTROPHIL FUNCTIONAL DEFICIENCY	
Chronic granulomatous disease (CGD)	Abscesses and infections of parenchymal organs and lymph nodes
Leukocyte adhesion deficiency	Apurulent infections, delayed cord separation and periodontitis
COMPLEMENT DEFICIENCIES	
Classical pathway deficiency	Sinopulmonary infections with/without systemic lupus erythematosus
Alternative pathway deficiency	Sinopulmonary infections
Both pathways deficient	Above plus neisserial infections
Mannan-binding lectin (MBL) deficiency	Sinopulmonary infections and recurrent *Candida* infections Especially important with concomitant primary or secondary immune deficiency, ICU and cystic fibrosis patients
IMMUNODEFICIENCY SYNDROMES	
Wiskott-Aldrich syndrome	Bacterial and viral infections, thrombocytopaenia with small platelets, eczema, lymphoma, autoimmunity
Ataxia Telangiectasia	Progressive ataxia, telangiectasia, immune deficiency
DiGeorge syndrome	Mostly no or mild immunodeficiency Occasionally severe SCID-like presentation/ cardiac defects/dysmorphism/low calcium

Hyper IgE syndrome	AD (autosomal dominant) form: Boils/ pneumatocoeles/eczema-like skin rash/ abnormal facies/failure to lose primary teeth AR (autosomal recessive) form: severe and recurrent herpes viral infection. Persistent/ recurrent molluscum contagiosum

Most primary immune deficiencies are caused by an antibody (B-cell) deficiency or a combined antibody and cellular (T-cell) deficiency. Isolated T-cell deficiencies, complement and phagocytic cell deficiencies are much less common.

RECOGNISE THE CLINICAL AND LABORATORY CLUES

Certain clinical and/or laboratory findings over a period of time, or certain immediate clues should be used to alert clinicians to the possibility of an underlying immune deficiency.

CLINICAL AND LABORATORY FINDINGS SUGGESTIVE OF A PRIMARY IMMUNE DEFICIENCY

- Persistent lymphopaenia ($< 1.5 \times 10^9$/L in older children and $< 2.5 \times 10^9$/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, e.g. complicated varicella

- Dependence on, or refractory to antibiotic treatment
  - Need for intravenous antibiotics to clear infection
  - Two or more months on antibiotics with little improvement

- Infectious syndromes
  - More than one organ involved
  - Recurrent deep skin or organ abscesses
  - Two or more serious infections, e.g. sepsis, meningitis, pneumonia

- Organisms
  - Infections caused by less virulent or opportunistic organisms
  - Persistent oral thrush or cutaneous candidiasis (especially in children older than four months)

- Constitutional symptoms
  - Persistent, extensive, atypical dermatitis or erythroderma
  - Chronic diarrhoea

- Examination findings
  - Lymph nodes and tonsils may be absent with a severe PID
  - Evidence of chronic ear infection
  - Evidence of bronchiectasis

- Family history
  - Primary immunodeficiency
  - Unexplained sudden death in infancy
  - Consanguinity

- Age and gender
  - SCID presents in early infancy
  - Profound antibody deficiency usually presents during the first year
  - Severe immune deficiencies 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

Any one of the following is typically regarded as suggestive of an underlying primary 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
- failure to thrive

In the South African context, disseminated bacillus Calmette-Guérin (BCG), paralytic poliomyelitis from oral polio vaccine, recurrent meningococcal infections, *Pneumocystis jirovecii* pneumonia in HIV-uninfected patients and infections with atypical mycobacteria are infections suggestive of a possible PID requiring further investigation. An acronym to assist with the awareness and diagnosis of PIDs was endorsed by the Primary Immunodeficiency Network of South Africa (PINSA), namely 'SPUR': Severe, Persistent, Unusual and Recurrent (SPUR) infections.

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

KNOW THE SENTINEL ORGANISMS

The type of organism can also provide clues as to the nature of the underlying immune deficiency. Infections with certain organisms, including infections with organisms that we find in the context of HIV infection, should prompt further investigation for a PID. A negative HIV test with or without a low CD4 count and an infection with 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 (IgA deficiency or CVID) may often have protracted diarrhea caused by the parasite *Giardia lamblia*. Patients with agammaglobulinaemia are especially susceptible to infections with enteroviruses, which may lead to chronic meningoencephalitis. 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 important clues that an underlying T-cell defect may exist.

Lymphadenitis and recurrent abscesses caused by low-virulence Gram-negative bacteria including *Escherichia coli*, *Burkholderia cepacia*, *Serratia* or *Klebsiella* and recurrent *Staphylococcus aureus* infection or invasive aspergillosis may indicate abnormalities in granulocytes such as chronic granulomatous disease.

TYPICAL INFECTIONS AND ASSOCIATED PRIMARY IMMUNE DEFICIENCY

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
Pneumocystis 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
Enterovirus meningoencephalitis	Agammaglobulinaemia or severe CVID
Recurrent infections with *Staphylococcus aureus*, coagulase-negative staphylococci, *Serratia marcescens*, *Chromobacterium violaceum* or *Aspergillus*	Phagocyte dysfunction
Recurrent staphylococcal skin infections, abscesses, lung cysts or pneumonia	Hyper IgE syndrome
Recurrent herpes virus 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, rotavirus, 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 non-tuberculous 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 (warts, hypogammaglobulinaemia, infection, myelokathexis) syndrome

BCG: Bacillus Calmette-Guérin; 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.

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 laboratory tests in consultation with a microbiologist to identify and treat infections appropriately in patients already diagnosed with a PID.

KNOW WHICH DIAGNOSTIC TESTS TO ORDER

A stepwise approach to the diagnosis of PIDs was proposed and developed by the Jeffrey Modell Foundation and modified for use in South Africa. 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 and not receiving immunoglobulin replacement therapy. A tiered approach should be followed and be directed towards the most likely immune deficiency as directed by the clinical history and examination.

A STEPWISE APPROACH TO THE LABORATORY DIAGNOSIS OF A PRIMARY IMMUNE DEFICIENCY

TEST	ASSOCIATION
FIRST-LINE INVESTIGATIONS	
Exclude HIV 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 immunoglobulin (Ig) G, M, A and E	Antibody and combined B/T cell deficiencies IgE should be tested in patients who may be at risk of hyper IgE syndrome
Cystic fibrosis (CF) screening	Suspected on history and clinical examination
Investigations for active TB	
SECOND-LINE INVESTIGATIONS	
Specific antibody response • Targeted to polysaccharide-specific antigens (*S. pneumoniae* and *H. influenzae*) 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 titres. Please note that an unconjugated pneumococcal vaccine, e.g. Pneumovax® should be given to determine an appropriate polysaccharide antigen response.
Lymphocyte subsets • B-cell numbers (CD19) • T-cell numbers (CD3). T-helper (CD4) and T-suppressor (CD8) cells should also be measured • Natural killer cells (CD16 and CD56)	Absent in XLA-linked agammaglobulinaemia when all immunoglobulin isotypes are severely reduced Reduced in T-cell defects, combined immunodeficiencies and occasionally CVID Isolated NK-cell deficiencies may be associated with recurrent herpes virus infections

Neutrophil function • Neutrophil oxidative burst • Neutrophil studies for leukocyte adhesion, chemotaxis and phagocytosis	Chronic granulomatous disease Leukocyte adhesion defects
Total haemolytic complement • Classic • Alternative	Complement deficiencies
THIRD-LINE INVESTIGATIONS	
Lymphocyte proliferation studies • Response to mitogens, e.g. phytohaemagglutinin, PMA, PMA + ionomycin, anti-CD3, anti-CD3 + IL2 or to recall antigens, e.g. *Candida*, tetanus, varicella	T-cell deficiencies including SCID, chronic mucocutaneous candidiasis
Neutrophil antibodies	Auto-immune 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 whole blood or dried blood spots – useful to do prior to giving live vaccines at birth
FOURTH-LINE INVESTIGATIONS	
• Cytokine studies • Enzyme studies • Genetic/molecular studies • T-regulatory cells • Th-17 cells • Surface markers for X-linked SCID • BTK (diagnosis of XLA) • MBL • NK cell cytotoxicity assay	Consult your local immunology pathologist

CONSIDER AN IMMUNE DEFICIENCY WHEN INTERPRETING ABNORMAL PATHOLOGY TESTS UNDERTAKEN FOR OTHER REASONS

Abnormal laboratory results may indicate a possible immune deficiency.

INCIDENTAL LABORATORY FINDINGS THAT MAY BE ASSOCIATED WITH A PRIMARY IMMUNE DEFICIENCY

LABORATORY RESULT	POSSIBLE CLINICAL IMPLICATION
BIOCHEMISTRY	
Low immunoglobulins	Humoral and combined immunodeficiencies Secondary immunodeficiencies
High immunoglobulins	May implicate HIV, autoimmune disorders, chronic inflammation and granulomatous disease
Coeliac disease serology	Specific IgA deficiency has a higher prevalence in patients with coeliac disease
High IgE (10 x upper limit for age)	Hyper-IgE syndrome, WAS, IPEX, DOCK-8 deficiency
Low IgE (< 2 IU/mL)	May represent antibody deficiency in ~7% of patients
Serum globulin gap	Antibody deficiencies can reduce the globulin fraction
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 papillomavirus 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, autoimmune haemolytic anaemia and autoimmune neutropaenia. ITP can be present in up to 6% of patients with CVID
Low platelet volume	This is strongly suggestive of the rare Wiskott-Aldrich syndrome
CYTOGENETIC TESTING	
A failed cytogenetic test (i.e. lymphocytes fail to proliferate after mitogen stimulation)	Consider a diagnosis of SCID

MICROBIOLOGY AND VIROLOGY TESTING	
Failed vaccine responses	Clinical episode of measles in a patient fully vaccinated. Failure to respond to hepatitis B vaccine (may occur in ~ 5% of the normal population) and rubella vaccination
Unusual or recurrent culture positive infections: • Recurrent *Streptococcus pneumoniae* and *Haemophilus influenzae* • Gastrointestinal infection with *Giardia lamblia* and *Campylobacter jejuni* • Recurrent or severe *Candida* infections • *Pneumocystis jirovecii* pneumonia • Recurrent, unexpected or severe viral infections, e.g. CMV, HPV	Refer to table 'typical infections and associated primary immune deficiency' above
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 *Giardia lamblia* infection which is a common infection in antibody deficiencies
Absence of plasma cells in biopsies	May be seen in humoral immune deficiencies

AIM TO IDENTIFY PATIENTS PRIOR TO THE ONSET OF CLINICAL SYMPTOMS

Newborn screening for severe primary immune deficiencies 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 will die before the age of one year. Research indicates that infants with SCID who receive haematopoietic stem cell transplants in the first three to four months of life have a better chance of survival as compared with infants receiving this treatment after this (95% vs. 76%). It is crucial to make this diagnosis as early as possible, before the patients receive live vaccines or present with infections, as live vaccines and infections can be fatal, as well as greatly diminish the success rate of the haematopoietic stem cell transplant.

Patients with XLA usually present later in life due to protective maternal antibodies, but are at great risk of developing infections after receiving live vaccines, such as oral polio, which can lead to fatal vaccine infections. These patients are also at risk for severe infections, especially pulmonary infections. Pulmonary complications are the most common cause of morbidity and mortality in

these patients. An early diagnosis of XLA can avoid the administration of live vaccines and ensure early initiation of immunoglobulin replacement therapy, which can prevent pulmonary and other infectious complications.

AIM TO MAKE A DEFINITIVE DIAGNOSIS

More than 250 genetic defects may result in a primary immune deficiency. Genetic testing can establish or confirm a suspected diagnosis and may predict future disease risk, inform reproductive decision making and guide appropriate treatment. One should be aware of testing limitations and patients and their families should be properly informed and counselled. A PID genetic panel is available in South Africa and covers the immunodeficiency diseases as summarised below.

IMMUNE DEFICIENCIES COVERED BY THE SOUTH AFRICAN PRIMARY IMMUNE DEFICIENCY PANEL

- Severe combined immunodeficiency (SCID)
- Hyper IgM syndrome
- Hyper IgE syndrome
- Immune dysregulation
- Common variable immunodeficiency (CVID)
- Lymphoproliferative syndromes, including autoimmune lymphproliferative syndrome
- Chronic granulomatous disease (CGD)
- MHC Class I and MHC Class II deficiencies
- Anhidrotic ectodermal dysplasia with immunodeficiency
- Autoimmunity with lymphoproliferation
- Antibody deficiencies
- T-regulatory cell defects
- Familial haemophagocytic lymphohistiocytosis (FHL), including FHL with hypopigmentation
- Chemokine signalling defects
- Innate immunity defects
- Complement deficiencies
- Isotype deficiencies
- Thymic defects with congenital abnormalities

If the PID gene panel is negative, further steps of exome and genome sequencing can be undertaken.

TRAINING OF PRE- AND POSTGRADUATE MEDICAL STUDENTS IN IMMUNOLOGY

Primary immune deficiencies is a growing field, however, there are only a few centres in Africa that offer specialised clinical immunology training. Proper training of doctors and nurses are linked to better patient care. Training in clinical immunology is therefore needed in order to facilitate a better and a more integrated approach.

REPORTING PATIENTS WITH A PID ON THE SA PID REGISTRY

The SA PID registry is part of a confidential research project. This registry helps create awareness of PIDs in South Africa and the information from this registry plays an important role for research and lobbying. The registry provides objective evidence needed to change policies, inform medical funders and improve patient outcomes through data sharing.