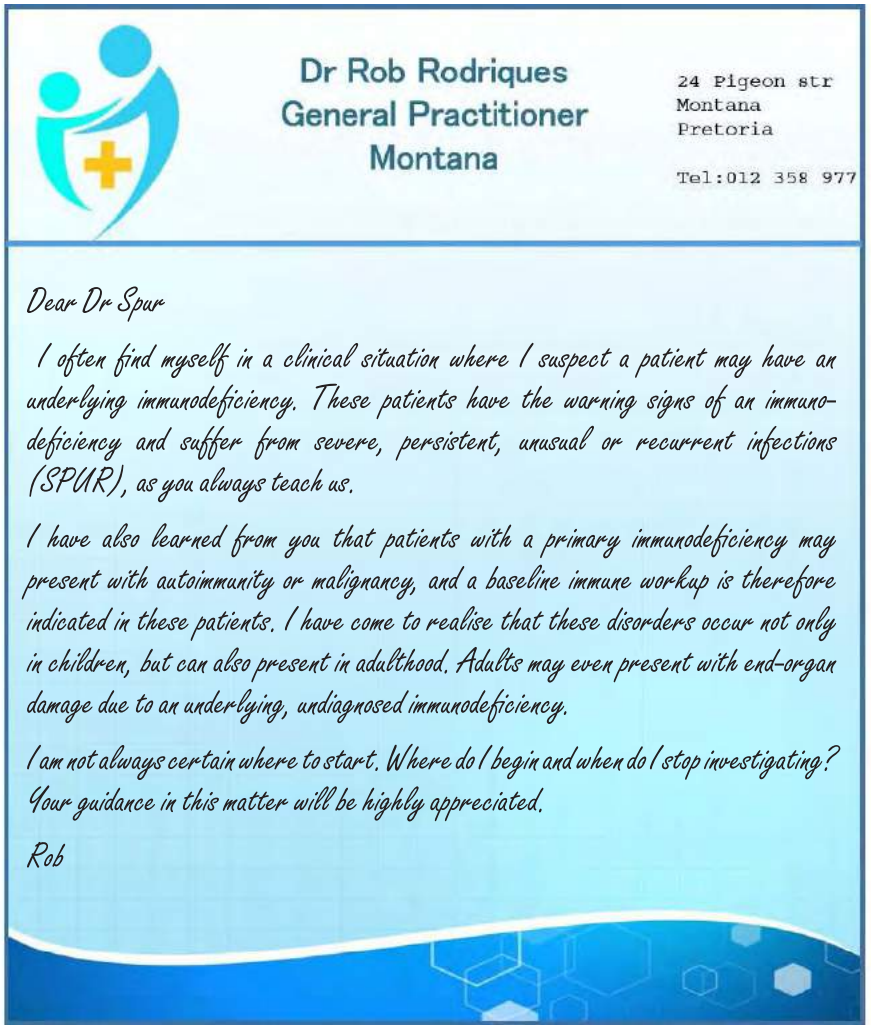
DR SPUR'S MYSTERY CASE

The case of 'what now?'

Welcome to Dr Spur's Immunology Clinic
Referral letter:



Dear Dr Rodriques

It is important to recognise a patient with an immunodeficiency in order to manage the patient appropriately and initiate treatment timeously. It cannot be emphasised enough that a high index of suspicion should always be maintained for possible immunodeficiencies, as untreated immunodeficiencies are life-threatening. Primary immunodeficiencies now form part of the disease group known as 'inborn errors of immunity'. These two terms are often used interchangeably.

I am therefore glad that you are thinking of immunodeficiencies, even in your adult patients. This is the most important step: recognising that these disorders exist and that they are not rare. According to a community-based study, the suggested prevalence of primary immunodeficiency disorders (PIDD) is 1 : 1 200. Forty per cent of these patients are diagnosed in adulthood when it is often too late. IgA deficiency has an even higher prevalence of 1 : 300. Slatter and Gennery made a very interesting statement that '… the question to be asked in a child presenting with recurrent infections is not "Who should be investigated for primary immunodeficiency?", but "What are the reasons for not investigating this child further?"'.[9] This is also true of adult patients.

Secondary causes of immunodeficiency include HIV infection, long-term corticosteroid use, leukaemia, lymphoma, nephrotic syndrome, malabsorption syndrome and an anatomical abnormality. These remain the most important reasons for immunodeficiencies and should always be differentiated from primary immunodeficiencies. A complete history and a physical examination should be accompanied by the necessary imaging and laboratory studies. Laboratory tests that may be of value to rule out secondary immunodeficiencies include:

- HIV serology
- full blood count
- renal- and liver-function tests
- lactate dehydrogenase (LDH)
- urine protein excretion
- stool alpha-1 antitrypsin (as a surrogate for intestinal protein loss)

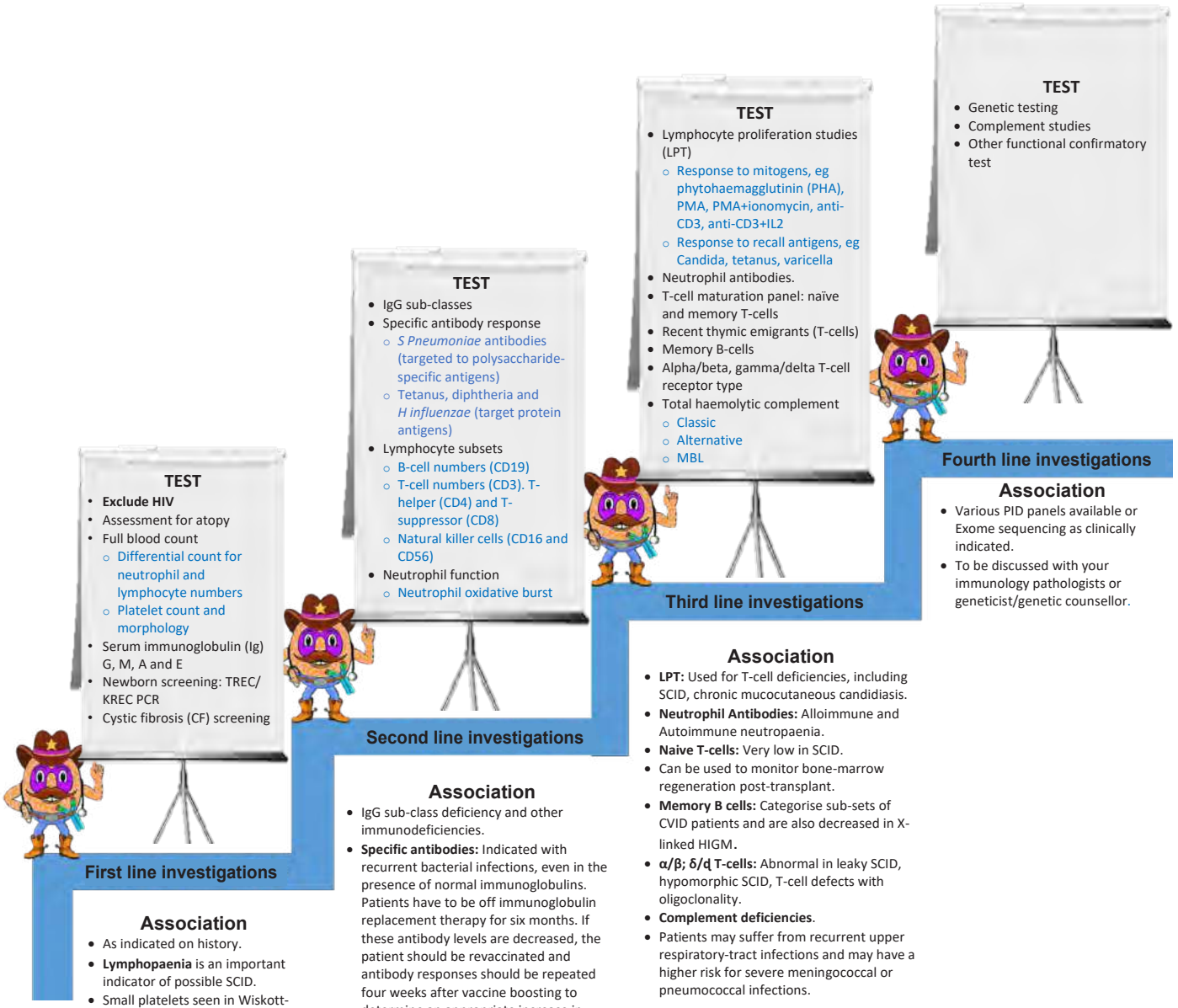


Figure 1: Stepwise approach to the laboratory diagnosis of PID

Adapted from Suchard, Buldeo & Van Rooyen,[6] Van den Berg & Van Rooyen,[7] Eley & Esser[8]

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; IL7Ra = Interleukin 7 receptor alpha; HIGM = Hyper IgM syndrome; IPEX: immune dysregulation, polyendocrinopathy, enteropathy and X-linked syndrome; FHL = familial haemophagocytic lymphohistiocytosis; WAS = Wiskott-Aldrich syndrome; HIGE = hyper-IgE syndrome; NEMO = nuclear factor-kappa ß essential modulator

- iron studies vitamin B12, folate, calcium, magnesium and phosphate
- serum protein electrophoresis with urine Bence Jones proteins.

A limited set of readily available laboratory investigations can be used to guide the initial work-up of primary immunodeficiencies. These investigations should ideally be used in a stepwise manner to screen, confirm, exclude other causes and classify the immune defect (see Figure 1). By doing first- and second-line investigations, which are cost-effective tests, many patients will be diagnosed timeously. This will lead to reduced suffering and improved quality of life (QoL). Repeat testing within 1–3 months is often necessary to avoid classifying post-infectious states as immunodeficiencies. Follow-up investigations after six months may also be necessary to look for waning immunity.

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

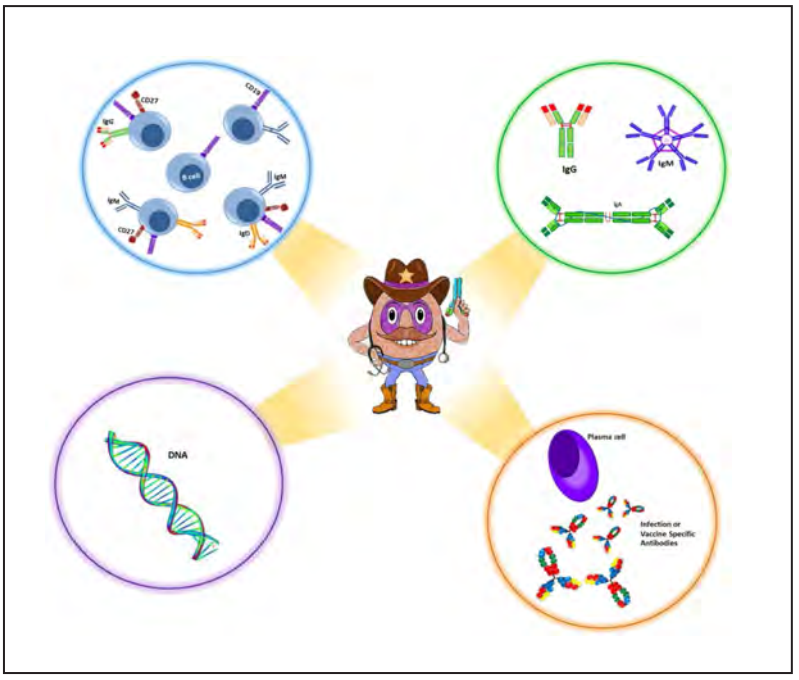


Figure 2: Diagnostic approach to investigating the humoral immune system
Adapted from Marsh & Orange.[1]

The initial investigations will often focus on the humoral immune system (see Figure 1) to exclude antibody deficiencies. These patients tend to present with recurrent bacterial infections of the respiratory and gastrointestinal tracts.

Serum immunoglobulin tests

Pitfalls in measuring immunoglobulins:

- Patients should be off immunoglobulin replacement therapy for six months.
- Values obtained for the different immunoglobulins must be compared with the expected laboratory values for age in all patients.
- Patients with immunoglobulin deficiencies may have false negative results from laboratory tests that measure antibodies in the blood – for example, anti-tissue transglutaminase IgA (anti-tTG) in IgA deficiency.
- The impaired antibody responses to pathogens in hypogammaglobulinaemic states may make the serological diagnosis of certain infections, such as HIV and EBV, difficult. In these patients, nucleic acid detection methods or cultures should be performed.

Persistent lymphopaenia

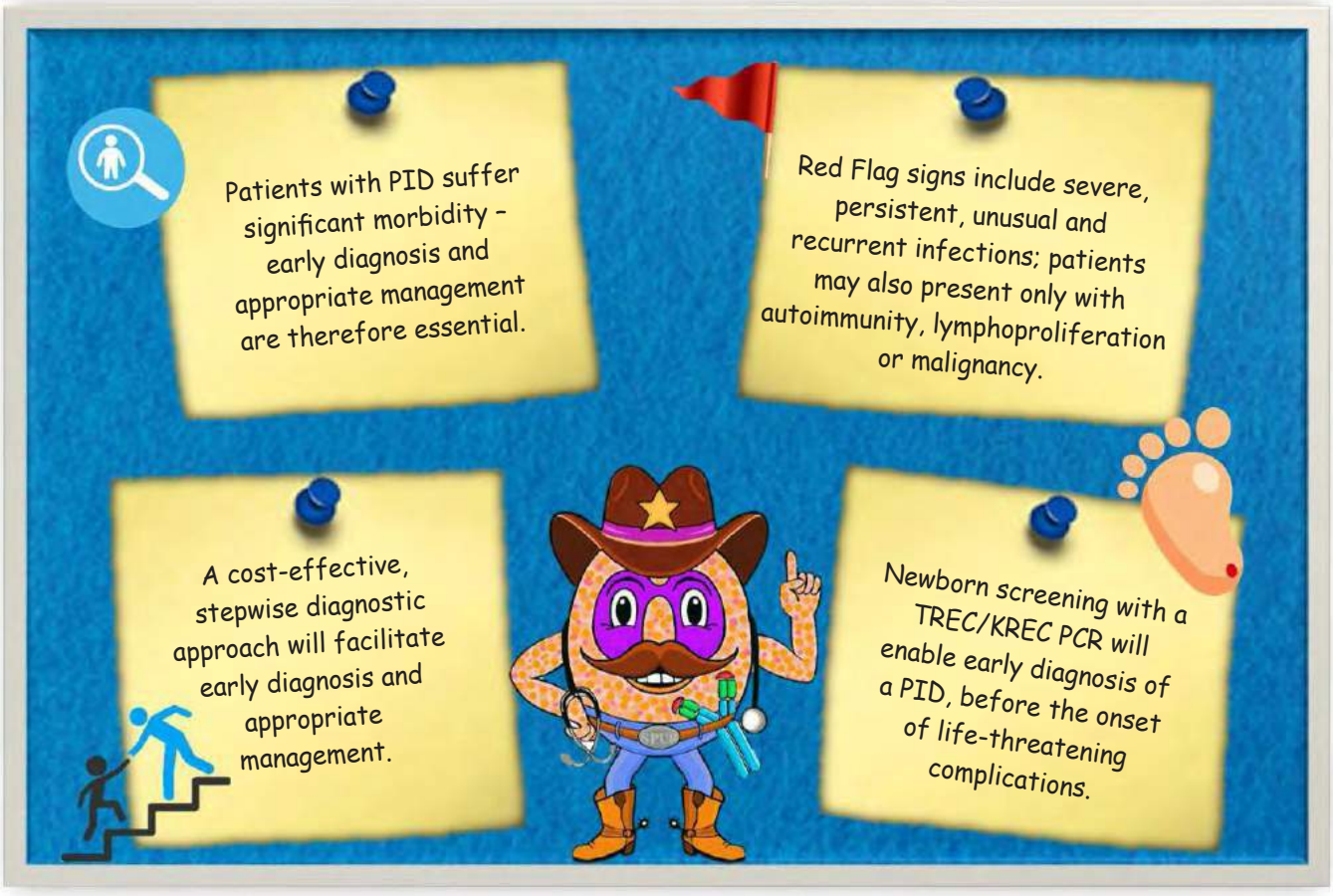
Persistent lymphopaenia (<1.5 × 10^9/l in older children and <2.5 × 10^9/l in younger children) should always be investigated in babies and young children, especially if there is a history of recurrent infections. This is a warning sign for a possible combined or severe combined immunodeficiency, which is a paediatric emergency.

Newborn screening

The goal of newborn screening (NBS) is to detect treatable disorders that are life-threatening or that cause significant morbidity before they become symptomatic. Severe combined immunodeficiency (SCID) is a life-threatening condition. Curative treatment is available if recognised early before the onset of infections: early stem-cell transplantation within the first 1–3 months of life gives babies the best chance of survival. Boys diagnosed with X-linked agammaglobulinaemia early, with prompt initiation of immunoglobulin replacement therapy, suffer less morbidity.

The TREC/KREC PCR is a highly accurate screening test for severe primary immunodeficiency disorders. The cost of this test is negligible when considering the severity of the illness that may result from a delayed diagnosis. TRECs are the best marker for the production of functional T-cells by the thymus, whereas KRECs are the best marker for the production of functional B-cells by the bone marrow. Both of these markers are combined in one screening assay. The reported sensitivity of this PCR screening test nears 100% with a specificity of 99.9%. Lifesaving vaccines, such as for polio and tuberculosis (TB), are routinely administered to newborns. These are live-attenuated vaccines, and the administration of these vaccines in babies with an underlying immunodeficiency may be detrimental. Parents should be informed of the risks involved and given the option to screen their child for primary immunodeficiency before live-attenuated vaccines are administered.

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

Take it step by step!

AUTHORS

Sylvia van den Berg[1,2], Cathy van Rooyen[1,2], André van Niekerk[2]

1 Department of Immunology, Ampath Laboratories, South Africa

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

ILLUSTRATORS:

Rinette Theron, Marlene Buitendach

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