



DR SPUR'S MYSTERY CASE

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Parkhurst Paediatric Clinic



Dr Crystal Nqobane

Dear Dr Spur

I realise that patients with primary immunodeficiency disorders (PID) may present with more than simply infections and that many genetic disorders of immune dysfunction are described.

In my paediatric practice, what do you think are the clues that I must watch out for and how can I make a diagnosis of PID in a timely manner?

In other words, what will clearly shout out 'PID'?

Thank you for your guidance as always.

Regards

Dr Crystal Nqobane



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Dear Dr Nqobane

Primary immunodeficiencies (PID) are now being referred to as ‘Inborn Errors of Immunity’ (IEI). Patients may present with five clinical phenotypes, including infections, autoimmunity, autoinflammation, allergy and malignancy. Some of these manifestations may be present simultaneously or follow in no specific order.

In my next five letters to you, I will focus on the five clinical phenotypes of IEI, starting with infections.

More than 500 IEI have been described and probably more than 300 of these patients will suffer from problematic infections at some stage. Infections that are more severe, more persistent, rare (or opportunistic) or more recurrent than expected should always prompt further investigations. The clinical presentation of IEI is highly variable; however, most disorders involve increased susceptibility to infection. In fact, many IEI patients present with common infections (such as sinusitis, otitis media and bronchitis) and these infections may go undetected in the primary-care setting. IEI may present at any age and their accurate and timely diagnosis requires a high index of suspicion and specialised testing. These cases sometimes do shout out at you, but often they only whisper.¹

The International Union of Immunological Societies classifies the IEI phenotypically into 10 tables (IUIS):^{2,3}

Figure 1

1	Immunodeficiencies affecting cellular and humoral immunity (severe combined immunodeficiency – SCID and combined immunodeficiency - CID)
2	Combined immunodeficiencies with associated or syndromic features
3	Predominantly antibody deficiencies
4	Diseases of immune dysregulation
5	Defects of phagocyte number or function
6	Defects in intrinsic and innate immunity
7	Auto-inflammatory disorders
8	Complement deficiencies
9	Bone marrow failure
10	Phenocopies of inborn errors of immunity

Sentinel Organisms

You were asking about cases that will alert you to an IEI. Certain types of organism are regarded as sentinel organisms (the alarm-makers) and can provide clues as to the nature of the underlying immune deficiency (see Table I).^{4,5}

Being well versed in local infectious diseases is paramount for effective IEI recognition, which makes well-trained local paediatricians crucial to diagnosing IEI early.⁶ Infections with certain organisms should trigger alarm bells. These include infections with organisms that we find in the context of HIV infection. A negative HIV test either with or without a low CD4 count accompanied by an infection by an unusual organism therefore does not equate to laboratory error or an insignificant finding – think IEI instead.⁶

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

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

Lymphadenitis and recurrent abscesses caused by low-virulence gram-negative bacteria may indicate abnormalities in granulocytes such as chronic granulomatous disease.^{4,5} These gram-negative bacteria may include *Escherichia coli*, *Burkholderia cepacia*, *Serratia spp* or *Klebsiella spp* and recurrent *Staphylococcus aureus* infection or invasive *Aspergillosis*.

Many new genetic mutations associated with innate immune defects have been described in recent years and these patients may suffer from severe viral infections, *Herpes Simplex virus*, encephalitis, pyogenic bacteraemia, staphylococcal infections in childhood and severe candidiasis, fungal infections or chronic mucocutaneous candidiasis.

Once an IEI is suspected, then, based on the infections, directed testing can be performed. There is, however, an overlap of infections due to defects in different pathways, and one often needs to follow a stepwise approach to investigate all the immunological pathways.

Diagnostic testing involves

- measuring serum immunoglobulin levels;
- assessing serum-specific antibody titres in response to vaccine antigens, lymphocyte proliferation assays, flow cytometry with enumeration of T-cells, B-cells, NK cells and memory B-cells, neutrophil function assays, stimulation assays for cytokine responses and complement studies.

Neonatal screening with T-cell excision circle (TREC) PCR can

TABLE 1: IMMUNE DEFICIENCIES AND ASSOCIATED PATHOGENS

Pathogens and infections	Associated PID
Recurrent sinopulmonary infections by encapsulated bacteria (<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> Type B, <i>Moraxella catarrhalis</i>)	B-cell disorders
Recurrent pneumococcal infections	Humoral, complement or innate deficiency
<i>Pneumocystis jirovecii</i> pneumonia	T-cell deficiencies including SCID, CD40 ligand deficiency
<i>Pseudomonas aeruginosa</i>	Severe phagocytic, humoral or T-cell deficiencies; also cystic fibrosis, neutropaenia and soft-tissue injury
Enteroviral meningoencephalitis	Agammaglobulinaemia or severe CVID
Recurrent infections with <i>Staphylococcus aureus</i> , Coagulase negative Staphylococci , <i>Serratia marcescens</i> , <i>Chromobacterium violaceum</i> , <i>Burkholderia cepacia</i> or <i>Aspergillus spp</i>	Phagocyte dysfunction
Recurrent staphylococcal skin infections, abscesses, lung cysts or pneumonia	Hyper-IgE syndrome
Recurrent herpes viral infections	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	Defects in intrinsic and innate immunity, for example MSMD
HPV	Defects in intrinsic and innate immunity: <i>Epidermodysplasia verruciformis</i>
Severe influenza, severe HHV6, disseminated vaccine strain measles, severe herpes viral infections (HSV, CMV, EBV), severe VZV, severe RNA/DNA viral infections	Defects in intrinsic and innate immunity: predisposition to severe viral infections
HSV encephalitis	Defects in intrinsic and innate immunity: herpes simplex encephalitis
Invasive candidiasis, deep dermatophytosis, invasive fungal infections	Defects in intrinsic and innate immunity: predisposition to invasive fungal diseases
Mucocutaneous candidiasis	Defects in intrinsic and innate immunity: predisposition to CMC
Pyogenic infections, staphylococcal infections during childhood, severe COVID-19	Defects in intrinsic and innate immunity: TLR defects with susceptibility to bacterial infections
Recurrent molluscum contagiosum and/or persistent/ extensive/recurrent warts	T-cell defect, innate immune defect or combined immune defect
Bacteraemia with encapsulated organisms, Trypanosomiasis	Other IEI related to non-haematopoietic tissues
Fulminant viral hepatitis, Whipple's disease	Other IEI related to leukocytes
EBV-driven lymphoproliferative disorders	FHL, diseases of immune dysregulation

BCG: *Bacille Calmette-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*; FHL: *Familial haemophagocytic lymphohistiocytosis*; HPV: *Human papilloma virus*; MSMD: *Mendelian susceptibility to mycobacterial disease*; HSV: *Herpes Simplex virus*; CMC: *Chronic mucocutaneous candidiasis*; TLR: *Toll-like receptor* (Adapted from reference⁵)

detect severe T-cell defects at birth, allowing early intervention, which could prevent vaccination with live vaccines and severe infections developing. By diagnosing a severe T-cell disorder at birth, you will be able to prevent these organisms from causing infections.

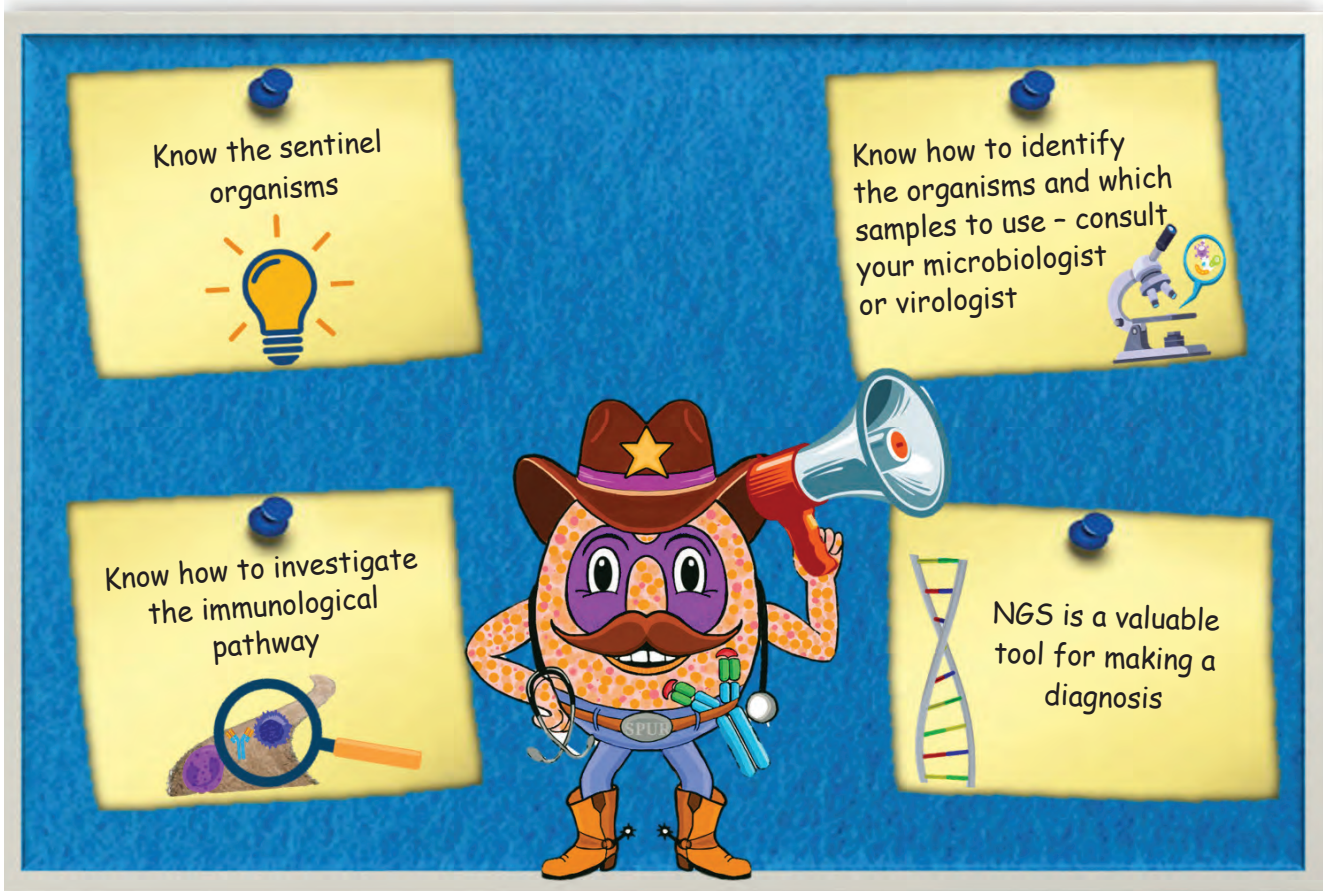
Similarly, B-cell excision circle (KREC) PCR can identify severe B-cell defects, including X-linked agammaglobulinaemia (XLA): these patients should not be administered live vaccines (eg polio vaccine) and need early immunoglobulin replacement therapy. Polio vaccine administration causes vaccine-associated poliomyelitis in patients with severe B-cell defects.⁶ Next-generation sequencing (NGS) allows many genes to be investigated simultaneously at a reasonable cost; this will

make possible the genetic analysis of more than 500 genes associated with IEI. Many IEI diagnoses are attained only through genetic testing.^{1,8}

Apart from raising the alarm about a possible IEI diagnosis, sentinel infections may also occur from time to time in known IEI patients. It is therefore important to have a high index of suspicion and to do appropriate cultures and PCR testing. Consultation with a microbiologist or a virologist will be of value to ensure that adequate sampling and testing procedures are followed in order to identify and treat infections appropriately.

These organisms should raise an alarm; listen to what they tell you.

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

Mystery case solved: knowing the sentinel organisms associated with IEI can help you with early diagnosis and management.

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