DR SPUR'S MYSTERY CASE

The case of the child who is always sick

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Paediatric Care

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Dear Dr Spur

I see many patients daily where the mother complains that the child is sick all the time.

Many of these children are toddlers, going to a crèche, or are babies with siblings attending a crèche or pre-school.

The symptoms also often overlap with allergy symptoms.

When should I start to think about a primary immune deficiency? Should I investigate all of these children?

Your guidance in this regard will be highly appreciated.

Kind regards
Dr Lindane

Dear Dr Lindane

Thank you for asking this very important question – it's one of many with which your clinical colleagues struggle.

The diagnosis of inborn errors of immunity is not always easy, especially among the many sick children general practitioners and paediatricians see in daily practice. These children can present with very common and non-specific complaints. Unless children are severely affected, the question always arises: When should I start investigating? Which tests should I request initially and when can I safely stop investigating?

In primary immune deficiency 'pattern recognition' of a constellation of clinical findings over a period of time, or certain immediate clues, has been used to alert clinicians as to the possibility of an underlying immune deficiency. A limited set of easily available laboratory investigations can then be used to guide subsequent work-up. The child with recurrent infections is a common scenario in clinical practice.

This may refer to infections that are:

- too frequent
- too severe
- too long lasting.

Or infections that:

- are associated with unusual complications
- fail to resolve with standard therapy.

The causes of recurrent infections are multiple, but can be grouped into four categories, based on frequency of occurrence (see Figure 1) in HIV-negative children:

- the **'normal'** child: 50% of occurrences in this cohort
- the **'atopic'** child: 30%
- the **chronically** ill child: 10%
- the child with **primary immunodeficiency (PID)**: 10%.

The 'normal' child: 50%

The 'normal' number of infections for a child will depend on various factors, including age and exposure. Infants and children vary considerably in the number of infections they experience. The average child has four to eight respiratory infections per year. Exposure to crèche or school going siblings may increase this rate to 9–10 infections per year. Poor nutrition, overcrowding and passive smoking may also increase the general predisposition to infection, including pyogenic skin infections, respiratory tract and middle ear infections. Most of the respiratory infections in these children are viral and they

TABLE I: FINDINGS SUGGESTIVE OF IMMUNE DEFICIENCY IN A CHILD

- Persistent lymphopaenia (<1.5 × 10/l in older children and <2.5 × 10/l in younger children)

- Unexplained excessive frequency and/or severity of infection, for instance:
  - Eight ear infections, two sinus infections per year (especially with mucopurulent discharge)
  - Two episodes of pneumonia in one year or chronic suppurative chest infection
  - Rare or unusual complications
    - complicated varicella, for example

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

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

- Organisms
  - Less virulent or opportunistic causative agent
  - Persistent oral thrush or cutaneous candidiasis (especially in children older than four months)

- Constitutional symptoms
  - Persistent extensive atypical dermatitis (AD) or erythroderma
  - Chronic diarrhoea

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

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

- Age and gender
  - Severe combined immune deficiency (SCID) presents in early infancy
  - Profound antibody deficiency usually presents in first year of life
  - 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 chest x-ray (CXR)

respond quickly to appropriate treatment, recover completely and appear healthy between infections. These children generally do not have more than one episode of pneumonia, or more than two episodes of uncomplicated otitis media in the first three years of life. Their physical examination and laboratory tests are normal and they have adequate growth and development.

The child with atopic disease: 30%

Chronic allergic rhinitis (AR) may be mistaken for chronic or recurrent upper respiratory tract infections. Children with atopic disease usually have normal growth and development. These children often develop coughing and wheezing following viral respiratory infections. Typical physical characteristics of atopy can be found on clinical examination, including allergic 'shiners' and a transverse nasal crease. Atopic children respond poorly to antibiotics but well to allergy or asthma medication. Positive allergy tests are diagnostic, but practitioners should be aware that immunodeficiencies and atopy may co-exist, including selective immunoglobulin A (IgA) deficiency, common variable immunodeficiency (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. These patients present with other symptoms and signs, and laboratory results are suggestive of their underlying chronic disease.

The child with PID: 10%

The child with a PID suffers from infections that are persistent, unusual, recurrent or serious, and they may not respond to conventional oral antibiotics. Failure to thrive is especially observed in patients with the more serious T-cell or neutrophil defects. Therefore, taking a comprehensive family history is essential and this should never be ignored or underestimated.

Infections are a key clinical feature, but patients may also present with autoimmunity, atopy or malignancies. A constellation of red-flag signs, in isolation or in combination, should prompt practitioners to look for an immune deficiency (see Table I).

Of the findings suggestive of PID, research found three to be the most important: a family history of a PID, including a history of an early infant death due to an infection, sepsis in children requiring intravenous antibiotics, and failure to thrive. In the South African context, bacillus Calmette-Guérin (BCG) dissemination, paralytic poliomyelitis following live polio vaccine, recurrent meningococcal infections, PJP (*Pneumocystis jirovecii* pneumonia) in HIV-negative patients and infections with atypical mycobacteria should be additionally highlighted warning signs.

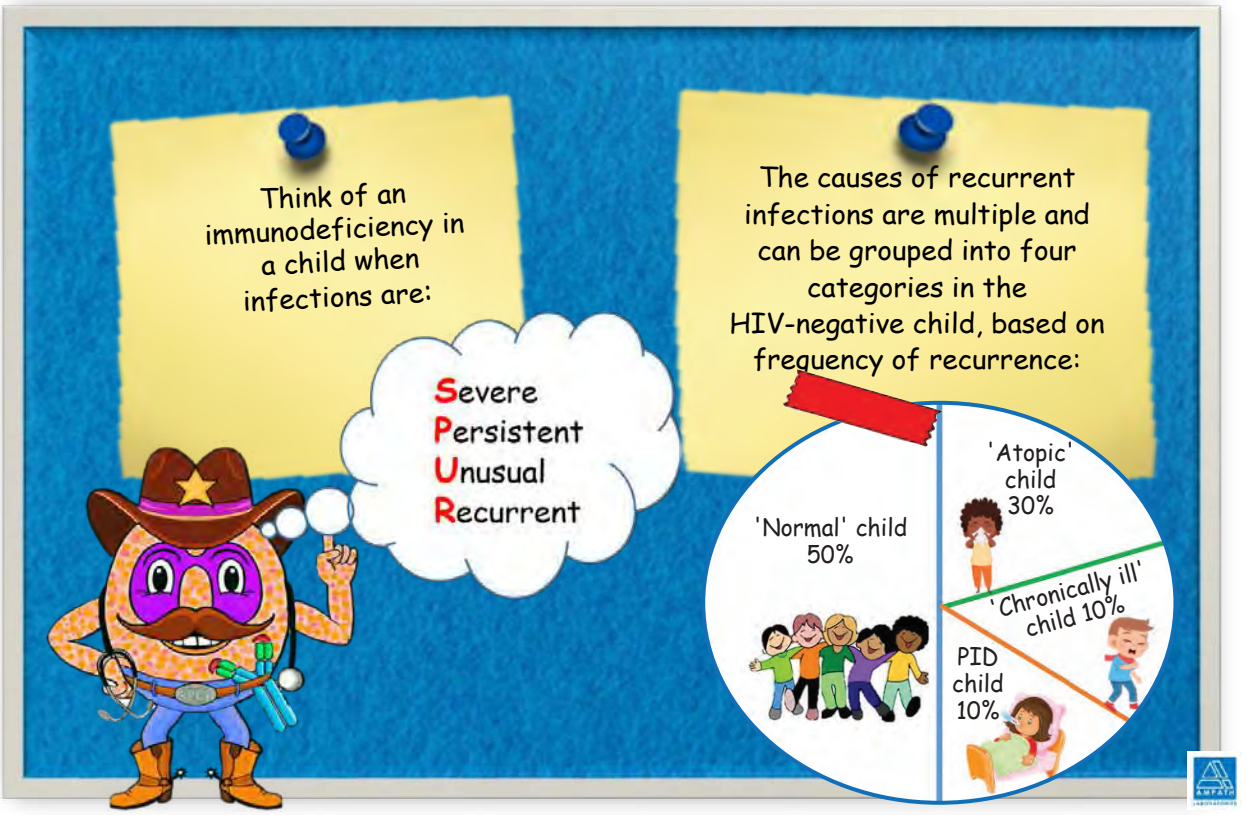
An acronym to help with diagnosing PID was endorsed by the Primary Immunodeficiency Network of South Africa (PINSA), namely, **SPUR: S**evere, **P**ersistent, **U**nusual and **R**ecurrent infections.

So, next time you are consulting a child with recurrent infections, think of me, Dr Spur ☺.

Yours truly

Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:
It's a case of SPUR

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