

PID123

Primary Immunodeficiency

SPECIFIC ANTIBODY DEFICIENCY (SAD)

Liesel is a ten-year-old girl. She has been attending Dr Goodheart's paediatric clinic since she was five; first, with recurrent respiratory infections and later with recurrent bacterial meningitis.

Liesel is an only child born into a mixed-race family living in the Cape. She has no known family history of recurrent infections. She was born with congenital deafness caused by a deformed cochlea. Her birth weight was average (3.2 kg) and she was breastfed for three-and-a-half years. She was fully vaccinated (including unconjugated polyvalent Pneumococcal vaccine and *Haemophilus influenzae* Type B [HIB] conjugate vaccine). Her neurodevelopment was normal and there were no dysmorphic features observed at the time.



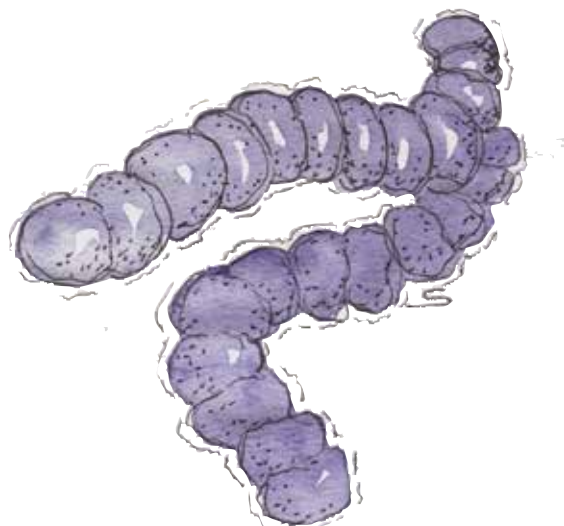
Liesel

Liesel was initially referred at age five years with a history of recurrent lower respiratory tract infections, which started at age two years. She had nine hospital admissions for pneumonia which resulted in lung damage with bronchiectasis. Presenting at age five years she was also failing to thrive. Some baseline investigations had already been done: two Mantoux tests and several TB cultures were negative, and she also tested HIV-negative. Other blood and sputum cultures were also negative. A 'sweat test' was normal, excluding cystic fibrosis – a relevant exclusion especially with recurrent respiratory infections in childhood.

Dr Goodheart requested a number of blood counts and immunological tests, as she considered some form of immune defect. Full and differential blood counts showed that white cells, red blood cells and platelets were within reference range, however, neutrophils were elevated. A phagocyte burst test done on flow-cytometry was normal, excluding Chronic Granulomatous Disease (CGD). Serum IgG was elevated and IgA, IgM, IgE were within reference range. B-cells, T-cells (CD4, CD8) were elevated, which may indicate a compensatory/

secondary response. NK cell count and the CD4 : CD8 ratio were normal. Due to the recurrence of bacterial meningitis, Dr Goodheart requested complement tests, but C3 and C4 were within reference range. At this stage Dr Goodheart could exclude X-linked agammaglobulinaemia (XLA; with peripheral B lymphocytes normal in number and with normal immunoglobulins), autosomal recessive agammaglobulinaemia (for the same reason as XLA), Hyper IgM syndrome (HIGMS, characterised by hypogammaglobulinaemia and normal or elevated serum levels of IgM), Common Variable Immune Deficiency (CVID; characterised by low serum IgG and IgA levels) and CGD (the neutrophil burst test normal). Two important culprits for complement deficiency, C3 and C4 were also normal.

Liesel was started on penicillin prophylaxis. Despite these precautions, she had a further episode of pneumonia. A lung (lingula) biopsy showed peribronchial chronic inflammation. She also started having recurrent episodes of meningitis. Cerebrospinal fluid cultures were positive predominantly for *Streptococcus pneumoniae* ('pneumococcus'; 6 ×) but also for *Haemophilus influenzae* (1 ×) and *Streptococcus pyogenes* (1 ×), amazingly without neurological impairment! She was investigated for skull defects and a cochlear malformation was discovered (Mondini dysplasia). Despite surgical repair of this, however, she developed further episodes of pneumococcal meningitis.



Nasty *S pneumoniae*

Liesel is now ten years old. Dr Goodheart feels that she is missing the diagnosis of an underlying immune defect. She consults her friend Dr Bala, an immunology specialist.

Dr Bala agrees that this is a difficult case and that Dr Goodheart has excluded a number of important causes. She decides to investigate for deficient vaccine responses as most of the infections appear to be bacterial and frequently related to *S pneumoniae*.

It turns out that *H influenzae B* antibodies are not protective pre- and post-vaccination. *S pneumoniae* antibodies are borderline protective despite recurrent documented infections and the levels do not increase after vaccination. *Clostridium tetani* and *Corynebacterium diphtheriae* antibodies, on the other hand, are protective.

Dr Bala explains to Dr Goodheart that deficient antibody responses especially to polysaccharide antigens may persist after infancy and result in recurrent respiratory infections despite normal levels of immunoglobulins, as in Liesel's case. She arrives at a preliminary diagnosis of **specific antibody deficiency (SAD)** (see Box). Liesel is started on intravenous immunoglobulins (IVIG) infusions three-weekly to prevent further infections.

Given her susceptibility to severe infections and already established bronchiectasis, Dr Bala recommends that Dr Goodheart should continue IVIG and penicillin prophylaxis long-term despite the lack of a confirmed genetic diagnosis. Liesel is currently thriving and doing well.

Recently Liesel also developed a left-sided foot drop and atrophy of the calf with a tarsal coalition of the foot for which immobilisation was applied. Whether the congenital deafness and the abnormal bone structure of the foot are related to her immune defect remains to be explored in the future with the help of the geneticists.

Box: Specific antibody deficiency (SAD)¹

SAD is a primary immunodeficiency disease (PID) characterised by:

- normal immunoglobulins, IgA, IgM, total IgG and IgG subclass levels;
- diminished antibody responses to polysaccharide antigens following vaccination; abnormal IgG antibody response to a pneumococcal vaccine;
- recurrent or severe bacterial infections (the sentinel pathogen is *S pneumoniae*);
- increased prevalence of atopy (allergies must be treated by standard interventions).

Practice points:

- Infections encountered in SAD mimic those in other PIDs; exclude Wiskott-Aldrich syndrome (WAS), Common Variable Immune Deficiency (CVID); T-cell deficits, etc.
- The diagnosis should not be conferred until after two years of age (by that time solid immune responses and robust responses to polysaccharide vaccines are typically reached in healthy children).
- Antibiotic prophylaxis is widely used to treat SAD and in selected cases IgG replacement therapy.

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REFERENCES

1. Perez E, Bonilla FA, Orange JS, Ballou M. Specific antibody deficiency: Controversies in diagnosis and management. *Front Immunol* 2017;8:586.