DR SPUR'S MYSTERY CASE
of an isolated IgA deficiency

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Kiddi Care Medical Centre

Dr Nash
Paediatrician

Dear Dr Spur

Thank you for seeing this patient.

Miss Botha is a 12-year-old girl with a history of recurrent infections from an early age and a probable diagnosis of IgA deficiency.

She presented with recurrent viral infections, recurrent otitis media, and frequent sinusitis with one positive culture of *S pneumoniae*. The episodes of sinusitis were often treated empirically without taking cultures. She was admitted once with pneumonia at the age of seven, with a positive culture for *H influenzae* type B. She had two episodes of Giardia lamblia gastro-enteritis, which cleared on Flagyl treatment.

She was fully vaccinated. There is a family history of allergy and autoimmunity. Her mother suffers from autoimmune thyroiditis (she is on thyroid hormone replacement), her father has a cat and grass allergy and her older brother has house-dust mite (HDM) allergy. She has no other medical conditions and she is not taking any chronic medication.

She went to pre-school initially, but her mother took her out, because she was sick every month while attending. When she stayed at home, she had less frequent infections. She attended school from the age of six years.

She experienced approximately seven episodes of respiratory infections annually, which were always treated successfully with antibiotics.

She had a tonsillectomy and adenoidectomy at the age of four and two sinus rinse procedures. Her laboratory work-up demonstrated persistently decreased IgA levels. Other investigations were unremarkable; she is HIV-negative and had the occasional elevated CRP level during episodes of infection, with a normal full blood count, normal protein and albumin levels and no urinary protein excretion.

Could you kindly advise on further management?

Do you think she should be receiving immunoglobulin replacement therapy to protect her during the COVID19 pandemic?

Kind regards
Dr Nash

Dear Dr Nash

Persistently decreased levels of IgA after the age of four years can be clinically significant in about 30% of patients. It is important to always exclude secondary causes for decreased IgA levels, including protein-losing conditions and drugs, especially anti-epileptic medication. Patients with IgA deficiency may present with significant upper and lower respiratory tract infections, which may lead to end-organ damage if not managed appropriately. They may also have concomitant allergic disorders and autoimmune disorders. IgA deficiency has been associated with abnormalities of antibody-mediated immunity, including IgG subclass deficiency and impaired antibody responses against both protein and polysaccharide antigens (specific antibody deficiency). IgA deficiency may also evolve into common variable immunodeficiency (CVID).

I tested her IgG subclasses and an IgG3 subclass deficiency was demonstrated. Her IgG3 level was 0.92 g/L (age-matched reference range 0.138–1.058 g/L). We also measured the quality of her humoral immune system by testing antibody levels to polysaccharide antigens (*S pneumoniae* serotype-specific antibodies) and protein antigens (*C tetani* antibodies). Her baseline *S pneumoniae* serotype-specific antibody levels (polysaccharide responsiveness) demonstrated that only 8% of her serotype-specific antibody levels were protective. At least 70% of the measured *S pneumoniae* serotypes should be above 1.3 ug/L in her age group. Her tetanus antibodies (protein responsiveness) demonstrated low levels of tetanus antibody levels; 0.8 g/L (age-matched reference range >0.1 g/L). She was subsequently revaccinated with Tetanus Toxoid vaccine to test protein responsiveness. She was also vaccinated with Pneumovax 23®. Pneumovax 23® is a non-conjugated vaccine and therefore tests polysaccharide responsiveness. Antibodies were measured six weeks post-vaccination and her tetanus antibodies increased to >2.4 g/L, therefore demonstrating more than fourfold elevation in protein antibody levels. This is satisfactory. However, she demonstrated protective levels of >1.3 ug/L to only 56% of the measured *S pneumoniae* serotype-specific antibodies. Polysaccharide non-responsiveness was therefore demonstrated. She had normal levels of class-switched memory B cells and a slightly decreased absolute CD4 count.

These markers are important to assess possible morbidity in patients with humoral immunodeficiency.

I made a diagnosis of an IgG subclass deficiency with associated IgA deficiency and specific antibody deficiency. It is important to note that one can make this diagnosis only after the age of four because some children manifest a delayed maturity of the immune system, a condition known as transient hypogammaglobulinaemia of infancy (THI).

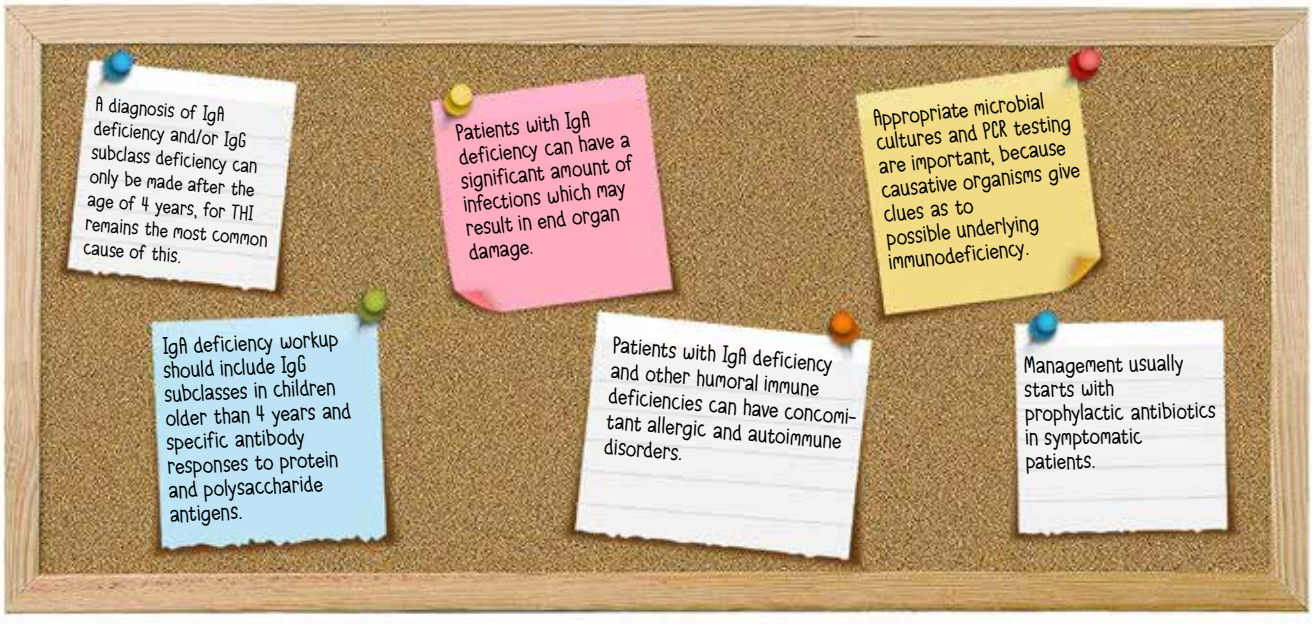
Management of this antibody deficiency syndrome usually follows a sequential approach to therapy until a satisfactory clinical response is obtained. The sequence consists of: (a) vigorous and early antibiotic treatment of infections; (b) prophylactic antibiotic treatment (once daily cotrimoxazole or azithromycin three times a week are useful in this context); and (c) lastly, immunoglobulin replacement therapy (IRT), if significant infections occur despite prophylactic antibiotics. This patient will most likely not have an allergic reaction if IRT is ever indicated, as she produces low levels of IgA. Patients with complete absence of IgA may very rarely experience allergic reactions, especially towards intravenous IRT. Kindly remember that if IRT is to be given, the IgA levels will mostly remain unaffected, because IRT does not contain IgA (only trace amounts) and only the IgG component is replaced. Immunoglobulin replacement therapy in the context of prevention of COVID-19 is not indicated, for the donor base will not have protective antibody levels at this moment in time and for the near future.

She should be followed up regularly, as this condition could evolve into CVID. Clinical history and examination remains important, because of the risk of developing autoimmune and allergic disorders, which need to be properly investigated and managed appropriately.

Thank you for the referral.

Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

A case of IgA deficiency with IgG subclass deficiency and specific antibody deficiency.

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