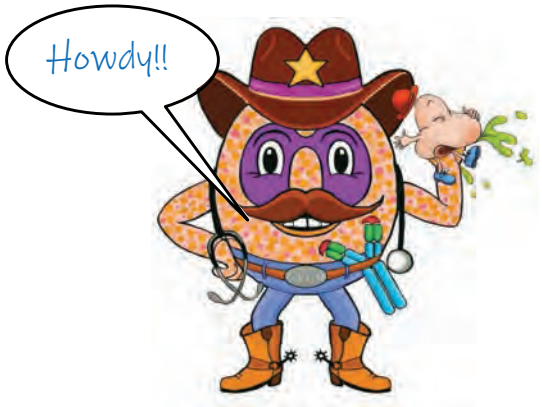


DR SPUR'S MYSTERY CASE

The Mystery Case of an Allergic Patient not Responding to Therapy

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Dr AC BRUNO

Ear Nose Throat Surgeon

Midlands Medical Centre
431 Kaleb str
Sandton
2196

Dear Dr Spur

I am treating a 17-year-old girl who suffers from chronic rhinosinusitis. She has had three sinus rinses, but her symptoms keep on recurring. When she was little, the GP told the family she has inhalant allergies and she has been using antihistamines twice a day with a corticosteroid nasal spray ever since. She is treated regularly with a course of antibiotics, which appears to relieve her symptoms transiently. I have done an allergy workup; skin-prick testing to all the common inhalants were negative. She was also negative for inhalants on basophil activation testing. In addition, she does not have the typical allergy symptoms of an itchy, runny nose, itchy eyes, allergic shiners or regular sneezing. I am beginning to suspect that something else is the matter with her. I started a brief immunologic workup. Her immunoglobulins and IgG sub-classes were all within normal limits. Her tetanus antibodies were normal and she had a total *Streptococcus pneumoniae* antibody value of 45 ug/mL, which was within the reference range.

Can you please assist with further investigations and recommendations?

Thank you for your valued opinion

Kind regards

Dr AC Bruno
Ear Nose and Throat Surgeon

Dear Dr Bruno

Thank you for referring this delightful young lady to my practice.

Her quality of life is definitely hampered by the recurrent episodes of sinusitis and by her feeling generally unwell. It is important to get to the bottom of this before permanent structural damage occurs.

I requested baseline *Streptococcus pneumoniae* serotype-specific antibodies and subsequently vaccinated her with a polysaccharide vaccine, Pneumovax 23®. I repeated the *S pneumoniae* serotype-specific antibodies four weeks later. She responded with a twofold increase to only three of the serotypes. A diagnosis of a moderate specific antibody deficiency (SAD) was made. I started her on prophylactic antibiotics. She should be monitored for breakthrough infections and, if severe rhinosinusitis recurs despite her being on prophylactic antibiotics, immunoglobulin replacement therapy should be considered.

Even though her total *S pneumoniae* antibody level was within the 'normal' range, it does not exclude antibody deficiency to specific *S pneumoniae* serotypes. Measurement of the total anti-pneumococcal IgG in a single test that produces a single numeric value, without differentiating specific antibodies to individual serotypes, is not always that useful.

It is common for patients with SAD to develop an increased antibody titre to a limited number of serotypes only, whereas antibody levels to most serotypes remain non-protective. Such a pattern cannot be elucidated by a test that does not distinguish between serotypes.

Assessing functional humoral immune status includes the baseline measurement of antibodies to tetanus and *S pneumoniae* serotypes. Antibodies to diphtheria and *Haemophilus influenzae* type B can also be measured. The patient needs to be revaccinated and antibodies repeated 4–6 weeks later to assess their functional immune response. Patients with a suspected immunodeficiency and normal baseline titres should also be revaccinated to assess the magnitude of the response as an x-fold increase.

Different vaccines are used to test different pathways of the immune system. The vaccines recommended for use in patients older than two years include:

- **23-valent purified capsular polysaccharide vaccine (PPV-23) Pneumovax 23®:**
  - Assess antibody production to polysaccharide antigens.
  - This tests T-cell-independent responses.

- **Tetanus, diphtheria with/without conjugated *H influenzae* vaccines:**
  - Assess antibody production to protein antigens.
  - These test T-cell-dependent antibody responses requiring T- and B-cell cooperation.

This process is called 'diagnostic vaccination' and is a safe and effective way of testing the functional status of the immune system.

In patients who did not receive Prevenar 13®, the vaccine response can be interpreted as follows:

- **Pneumovax 23® polysaccharide immunisation (PPV) post-vaccination titres:**
  - As many serotypes as possible should be measured.
  - Use the same laboratory to assess baseline and follow-up values, because there is significant variation between laboratories.
  - A *S pneumoniae* serotype-specific level of 1.3 µg/mL is considered to be protective following vaccination.
  - If the baseline level is > 1.3 µg/mL, a twofold response is considered to be acceptable.
  - In levels well below the protective level, fold is irrelevant, but a response above the protective level is required.
  - A protective response in > 50% of the serotypes in children < 6 years and a > 70% serotype response in patients > 6 years is required.
- **Tetanus/diphtheria/conjugated *H influenzae* post-vaccination titre:**
  - A fourfold increase above baseline is considered to be a normal response. Tetanus toxoid is a very immunogenic vaccine; therefore, patients not responding to this protein antigen should be investigated for a more serious immunodeficiency, including common variable immunodeficiency and combined immunodeficiency.

In patients suspected of having SAD, there are four response phenotypes:

- **Severe phenotype**
  - Patients produce protective antibodies to two or fewer serotypes.
- **Moderate response phenotype**
  - Patients ≥ 6 years respond to at least three serotypes but < 70% serotypes are protective.
  - Patients ≤ 6 years respond to at least three serotypes but < 50% serotypes are protective.
- **Mild response phenotype**
  - Failure to generate protective titres to multiple serotypes or failure of a twofold increase in 70% of serotypes in patients ≥ 6 years.
  - Failure to generate protective titres to multiple serotypes or failure of a twofold increase in 50% of serotypes in patients ≤ 6 years.
- **Memory phenotype**
  - Patients respond adequately initially, but after six months protection is not sustained in > 50% of serotypes in patients < 6 years and in more than 70% of serotypes in patients > 6 years.
  - Therefore, if a normal response is obtained, antibody levels should be followed up in six months' time to assess the extent of the waning of immunity in patients with continuing infections.

Please note that there is biological variability in patients' response to polysaccharide vaccination.

SAD is a common primary immunodeficiency disorder of the humoral immune system (B-lymphocytes) and is defined as an insufficient antibody response to polysaccharide antigens in the setting of recurrent infections. Patients have normal immunoglobulin levels and normal responses to protein antigens. The diagnosis can be made only in patients two years and older, because younger children may have delayed physiological maturation of their T-cell independent antibody formation. Up to 15% of children with recurrent infections, who are undergoing immunologic evaluation, are diagnosed with SAD. SAD may also be diagnosed in adolescents and adults. In one study, the diagnostic criteria of SAD were met in 12% of adults with refractory chronic rhinosinusitis. In adolescents and adults, SAD is less likely to resolve over time; this is in contrast to children, who often improve after three years.

Patients with SAD have infections that are more frequent, severe or prolonged, and they may suffer from chronic and recurrent otitis media, sinusitis, bronchitis or pneumonia. Fewer than 5% of patients with SAD experience invasive infections. Patients may present with bronchiectasis or severe refractory sinusitis, especially adolescents and adults. They therefore need to be followed up regularly. Pathogens often identified in patients with SAD include the encapsulated bacteria *Streptococcus pneumonia*, *H influenzae* and *Moraxella catarrhalis*. *Staphylococcus aureus* and respiratory viruses can also be the presenting pathogens.

It is common for patients with SAD to present with symptoms resembling atopic diseases, including rhinitis and asthma. Chronic rhinosinusitis is commonly blamed for allergic disorders. But there are some helpful hints to distinguishing between these two possibilities. In patients suffering from a specific antibody deficiency:

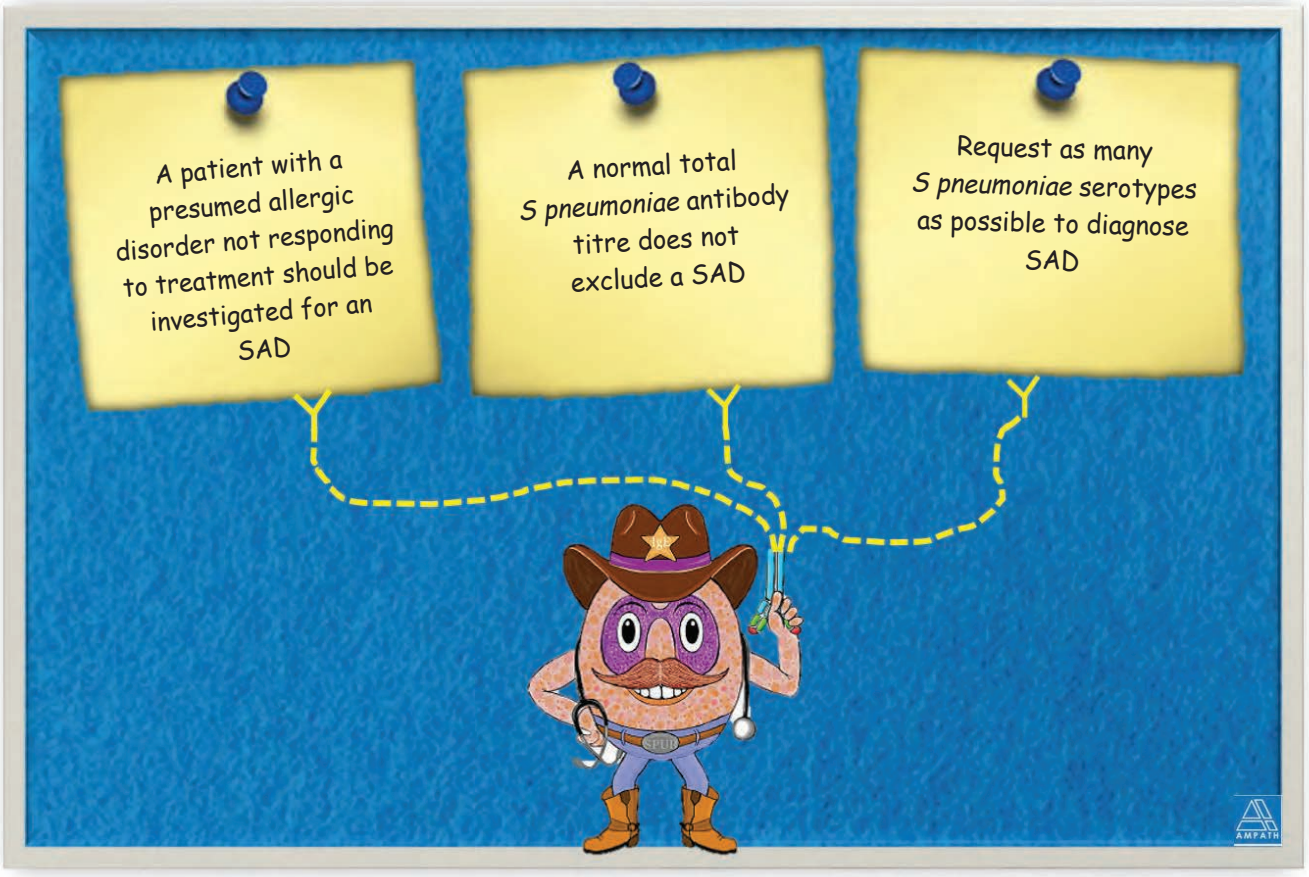
- a purulent nasal discharge occurs often;
- allergy testing is usually negative and allergic triggers cannot be identified;
- there is an absence of itchy, watery eyes;
- there is infrequent sneezing and itching of the nose;
- there is little improvement with allergy treatment and allergen avoidance;
- patients have a frequent wet cough as opposed to the classic dry cough of asthma;
- chest symptoms do not improve with inhaled bronchodilators;
- improvement with antibiotic treatment is transient.

The management of symptomatic patients with SAD should include a consideration of antibiotic prophylaxis and

appropriate antibiotic treatment of any bacterial respiratory infection. Treatment with high doses of antibiotics for a period of at least two weeks is often required. Immunoglobulin replacement is indicated for patients with mild, moderate or memory phenotypes who experience persistent infections despite appropriate management.

Kind regards
Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

It's SAD, it's not an allergy!

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