DR SPUR'S MYSTERY CASE

New symptoms in a patient with selective IgA deficiency

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Dr J Smith

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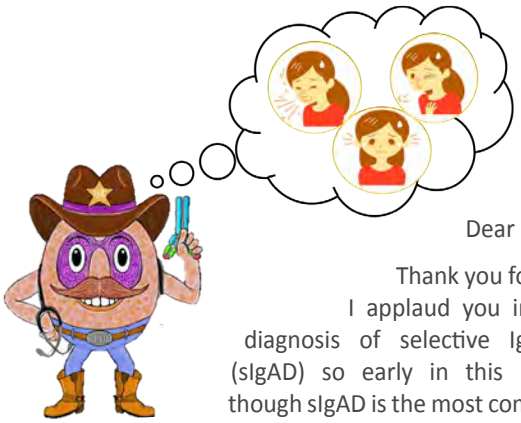
Dear Dr Spur

A seven-year-old Caucasian girl known to my practice was diagnosed with selective IgA deficiency (sIgAD) two years ago, after recurrent episodes of sinopulmonary infections. Her serum IgA level at the time was <0.07 g/L, with normal IgG and IgM levels and normal vaccine antibody responses. Other causes of IgA deficiency were excluded. She has been doing well on seasonal prophylactic antibiotics and remained infection-free for a year. However, over the past few months her mother noticed frequent episodes of sneezing and a persistent nasal discharge.

One month ago she presented to me with an episode of sinusitis which did not respond to conservative management and required antibiotic therapy. At today's follow-up visit she appeared in good general health. She had normal vital signs and a temperature of 36.3 °C. On examination, her nasal turbinates were pale and oedematous, and clear rhinorrhoea was noted. On further enquiry, her mother says that she wakes up with a runny nose and her symptoms are definitely worse in the mornings. She also complains of an itchy nose.

Her history and clinical features are highly suggestive of allergic disease. Do you perhaps have experience with sIgAD patients that present with features of atopy? If so, please could you provide further guidance?

Yours sincerely
Dr Smith



Dear Dr Smith

Thank you for the referral. I applaud you in making the diagnosis of selective IgA deficiency (sIgAD) so early in this patient. Even though sIgAD is the most common primary immune deficiency (PID), it is often underdiagnosed.[1] This is because most patients with sIgAD are completely asymptomatic, possibly due to a compensatory increase in secretory IgM.[2] These patients are usually diagnosed by chance when serum immunoglobulins are requested. The European Society for Immunodeficiency (ESID) defines sIgAD as serum immunoglobulin A (IgA) levels below 0.07 g/L in patients older than four years of age with normal IgG and IgM levels, normal vaccine responses and the exclusion of secondary causes of low IgA levels.[3] Secondary causes include certain medications, viral infections, systemic diseases and chromosomal abnormalities.[1,2] Medication known to cause low IgA levels are glucocorticoids, angiotensin-converting enzyme (ACE) inhibitors, anti-malarial, anti-epileptic, anti-rheumatic and non-steroidal anti-inflammatory drugs (NSAIDs).[1, 2]

Based on the clinical presentation, sIgAD patients may be classified into different clinical phenotypes.[4] However, this is not always possible because fewer than 30%[2] of patients with sIgAD present with clinical symptoms. Apart from infectious diseases, sIgAD patients may present with autoimmune diseases, malignancies and/or allergic diseases.[2] The most common allergic conditions associated with sIgAD are allergic conjunctivitis, allergic rhinitis (AR), chronic urticaria, atopic dermatitis, asthma and food allergy.[1,2] Owing to the association of sIgAD with allergic diseases, patients should be monitored closely for allergy symptoms, especially if there is a family history of atopy.[2]

Uncertainty exists about the association between allergic diseases and sIgAD, in part because both are high-prevalence conditions.[2] The prevalence also seems to be population-specific, as studies from different countries have produced inconsistent results.[4] An allergic disease may be the first and/or only clinical manifestation of sIgAD[4] or sIgAD patients may develop an allergic disease during the course of their illness.[1,2] Some controversy exists whether allergic disease may predispose patients to sIgAD (i.e. allergic disease weakens mucosal membranes, which leads to secondary IgA deficiency) or is a complication secondary to sIgAD (i.e. IgA deficiency promotes the development of allergic disease).[2,4]

There are a few hypotheses to explain why patients with sIgAD are more prone to developing allergic diseases. In order to explain these, a brief review of the pathogenesis of sIgAD is necessary. Selective IgA deficiency (sIgAD) is caused by a defect in the immune system that leads to the reduced production of IgA. The mechanisms by which this occurs include defective class switching, defective maturation of B cells into IgA-secreting plasma cells,[1] impaired helper T cells and abnormal cytokine signalling.[2] IgA is present in the body as serum IgA and secretory (mucosal) IgA. Patients with sIgAD are deficient in both types of IgA. Serum IgA helps to prevent the circulation of allergens.[1] It acts by binding Fc alpha receptors I (FcαRI) on different cell types, including eosinophils and neutrophils.[4] Upon binding, it activates anti-inflammatory pathways. IgA has also been shown to induce the expression of IL-10, an anti-inflammatory cytokine. Furthermore, atopic patients with sIgAD have been shown to have a reduced ability to inhibit the proliferation of Th2-cells. Th2-responses are involved in the pathogenesis of allergic diseases.[4]

Secretory IgA is the first line of defence to prevent the entry of allergens through mucosal surfaces.[1,4] Studies show that secretory IgA can adsorb food antigens, agglutinate bacteria and neutralise toxins.[4] If secretory IgA is not present, foreign material such as allergens and bacteria may pass through the mucosa of the gastrointestinal and the respiratory tracts.[2] Autoimmune diseases associated with sIgAD (such as coeliac disease and inflammatory bowel disease (IBD)) may also increase gastrointestinal mucosal permeability by damaging the intestinal mucosa.[2] Once food antigens and aeroallergens pass through the mucosal defences and enter the circulation, severe allergic disease may occur.[2] Interestingly, the severity of allergy symptoms in children with sIgAD seems to correlate with the degree of IgA deficiency in the neonatal period.[4]

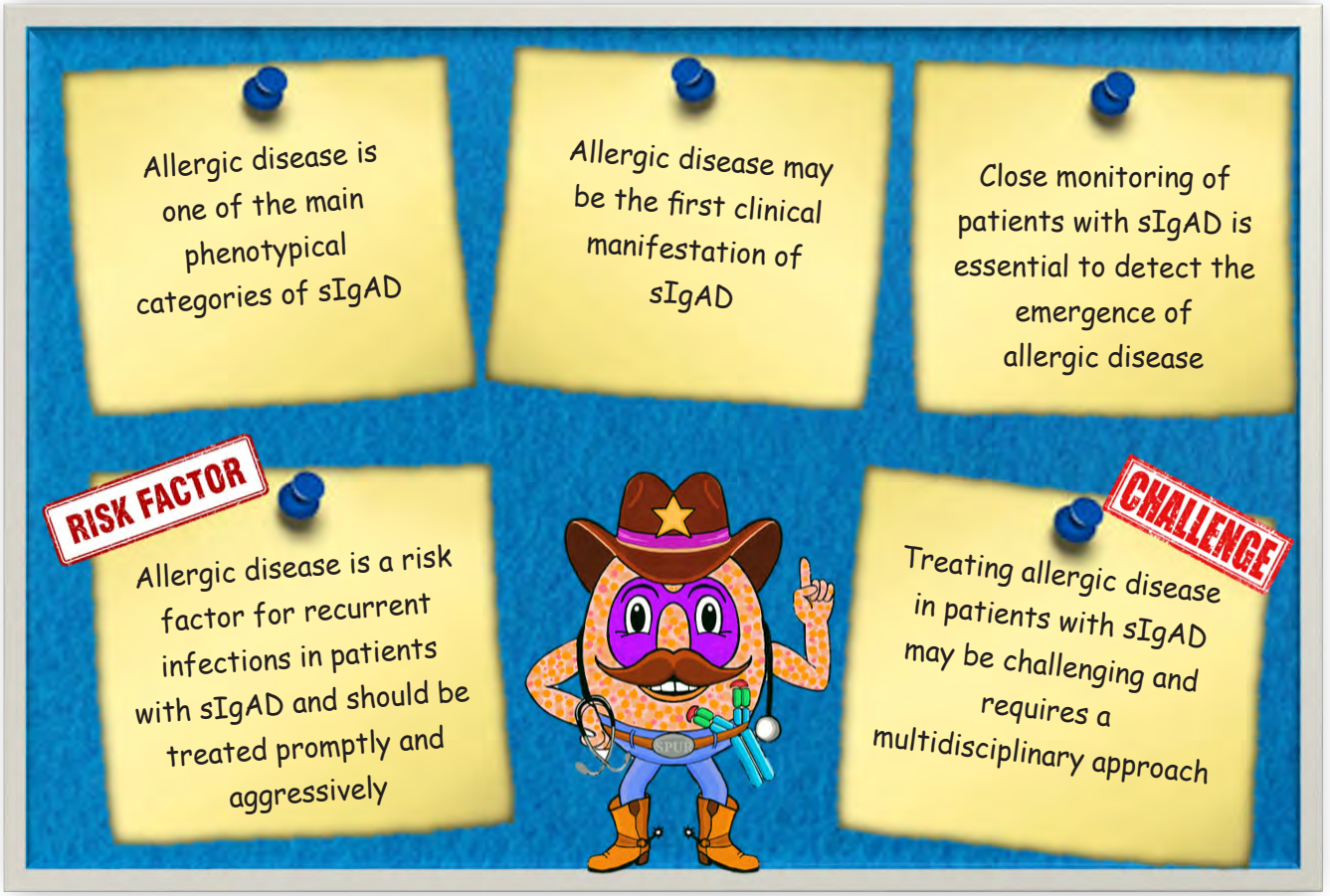
This brings us back to your patient. The symptoms that you are describing in this case do indeed suggest an allergic disease, specifically AR. Patients with AR typically present with sneezing, rhinorrhoea, nasal itching and congestion.[5] To support the diagnosis of AR, I requested the laboratory to perform an immunoglobulin E (IgE) food and inhalant allergy screen. The inhalant screen was positive; and when the specific IgE components were measured, it was found that the patient is sensitised to the house-dust mite (HDM) Dermatophagoides pteronyssinus. Although the treatment of AR in sIgAD is based on current standards of care,[1] it should be treated aggressively, considering that allergy-related inflammation may promote the development of respiratory tract infections.[4]

In this case, treatment is therefore especially important to improve control of the patient's sIgAD and prevent recurrent infections. Standard treatment modalities include environmental control measures (allergen avoidance), medication and possibly immunotherapy.[5] The treatment of allergic disease in sIgAD patients may prove to be more difficult compared to the general population, and symptoms may persist despite standard therapy. In such cases, the use of biological drugs may be considered.[4]

Sincerely

Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

A case of allergic rhinitis in a patient with selective IgA deficiency

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