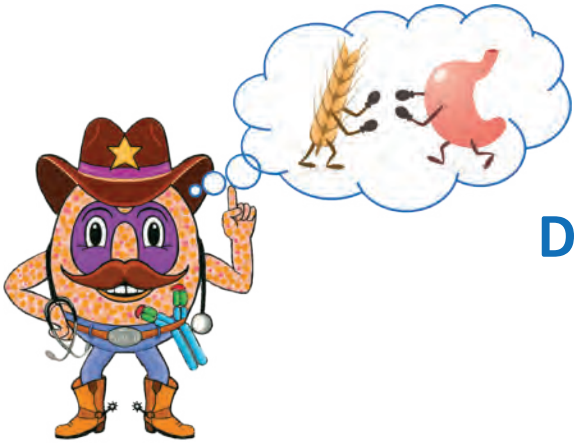


DR SPUR'S MYSTERY CASE

The pain of the grain ...

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Dr A.L van Rijn

Gastroenterologist

Suite G14
Medical Centre
Universitas Private hospital
Logeman St, Bloemfontein
9301
Tel: 051 444 6240

Dear Dr Spur,

Please assist me with the work-up of this young lady. Ms SS is a 22-year-old woman presenting with a long-standing history of intermittent abdominal pain, chronic diarrhoea and two previous episodes of Giardiasis, for which she was treated. According to her medical history, she has been treated for numerous sinusitis episodes by her general practitioner. She had grommets inserted as a child and suffers from prolonged lower respiratory tract infections, especially during winter.

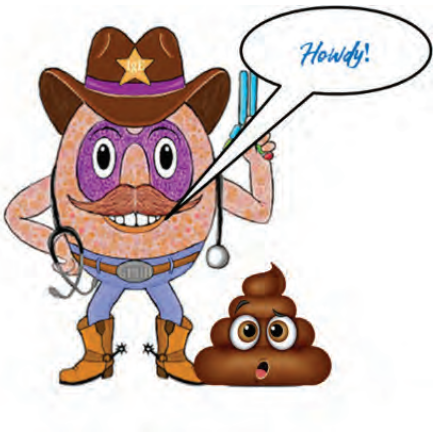
Clinically she is underweight and anaemic. She informs me that she has exhausted her sick leave at work due to multiple episodes of diarrhoea, malaise and general tiredness. I started with the serological investigation for coeliac disease and booked an endoscopy, but decided at the last minute to ask for immunoglobulin levels based on her history of recurrent infections.

Results:

T Transglutaminase IgA	0.0	0.0–6.9	U/mL
Gliadin IgA	0.4	0.0–6.9	U/mL
Endomysium IgA	Negative		
Endomysium IgG	**Positive**		
T Transglutaminase IgG	**40**	**0.0–6.9**	**U/mL**
Total IgA	**<0.07**	**0.70–4.00**	**g/L**
Total IgG	6.01	7.00–16.00	g/L
Total IgM	1.30	0.40–2.30	g/L
S Pneumonia antibody serotypes	70% Protection		
H Influenza	2.1		mg/L
Tetanus antibodies	1.3		IU/mL

The positive coeliac serology fits in with her clinical symptoms, but to my surprise she has absent IgA levels! Please help me with further management based on these findings.

Kind regards
Dr van Rijn



Dear colleague, this is indeed an interesting case and a few thoughts spring to mind. I am pleased that you considered assessing her immune system, as her infection history of **S**evere, **P**ersistent, **U**nusual and **R**ecurrent infections ticks all the boxes of Dr **SPUR**!

Selective IgA deficiency (sIgAD) is in fact the most common humoral immune deficiency and approximately 8% of patients with sIgAD also have coeliac disease (CD) – in contrast to the incidence of ~1% of CD in the general population.[1,2]

The European Society for Immunodeficiencies (ESID) classifies sIgAD as total serum IgA of <0.07 g/L with normal total IgG and IgM in a patient older than four years of age. A probable diagnosis of IgA deficiency can also be considered if the total IgA is at least two standard deviations below normal for age, with normal IgG and IgM.[3]

Always remember to exclude any secondary causes of IgA deficiency, such as glucocorticosteroid use, viral infections, systemic disease and other medication.[1,3]

Although the majority of patients with sIgAD are asymptomatic, the following symptoms should prompt a clinician to investigate the immune system further:[1,4]

- Recurrent sinopulmonary infections
- Autoimmune disease
- Gastrointestinal disorders and infections
- Allergic disorders (i.e. allergic conjunctivitis, allergic rhinitis (AR), chronic urticaria, atopic dermatitis (AD), asthma and food allergy)
- Anaphylactic transfusion reactions

IgA plays a crucial role in mucosal surface health and, interestingly, patients with sIgAD suffer more from recurrent respiratory tract infections than from gastrointestinal tract infections. This is believed to be due the fact that secreted IgM from mucosae compensate for the absence of IgA and is secreted more frequently in the gut.[1,3]

Coeliac disease

CD is an immune-mediated multisystem disorder triggered by the consumption of gluten (found in wheat, rye and barley) in genetically predisposed people. CD affects people of all ages but is more commonly seen in females. The genetic predisposition is well established to be in the HLA gene – HLA DQ2 and HLA DQ8.[5]

Most adults (>95%) will present with non-classic symptoms, almost exactly like your patient, and the diagnosis is often delayed (refer to Table I). A histological assessment of the small bowel is almost always necessary to evaluate the degree of villous atrophy and inflammatory infiltration of the duodenal mucosa.[5]

Pitfalls in serological testing

Most patients with CD produce IgG and IgA antibodies that recognise gliadin and/or the enzyme responsible for the deamination of gliadin – tissue transglutaminase (TTG). In cases where IgA is absent or very low, the result can be false negative and IgG-based serological testing is crucial.[5,6]

CD and sIgAD – what are the chances?

CD is associated with multiple other pathologies, including various autoimmune diseases, inflammatory bowel disease (IBS), Down syndrome, AD, gastro-oesophageal reflux disease (GERD) and sIgAD.[5]

There are a few hypotheses to explain why an autoimmune disease is associated with a humoral immunodeficiency. Some of these are:[6]

- impaired negative selection during B-cell maturation in patients with a humoral immunodeficiency, leading to the development of autoantibodies;
- genetic factors, leading to both a predisposition to autoimmune disease and immunodeficiency disorders (HLA associations);
- molecular mimicry, that is, foreign material (allergens and bacteria) passing through the disrupted mucosa of the gastrointestinal and the respiratory tracts;
- abnormal T-cell regulation, leading to a breakdown in immune tolerance.

What now?

Dietary counselling to implement a lifelong gluten-free diet (GFD) is crucial. The only treatment for CD is eliminating the offending protein, namely, gluten.[5,7] Most importantly, the patient should be monitored with IgG-based testing for adherence and response, not IgA-based serology.[8] TTG IgG monitoring is suggested.

Supplementation to correct nutritional deficiencies is recommended.

Most patients with partial IgA deficiency are asymptomatic and require no treatment. In patients with recurrent infections, prophylactic antibiotics (either continuously or seasonally) are advised.[4]

I suspect that her overall health will improve on a GFD as her nutritional deficiencies are restored and the inflammatory process resolves.

If you find that she is still suffering from repeated infections, a trial of immunoglobulin replacement therapy could be suggested – it does not replace serum IgA but rather provides

TABLE I: SYMPTOMS OF COELIAC DISEASE		
Classic (<5 years)	**Non-classic (most common)**	**Subclinical (silent)**
Chronic diarrhoea	Non-specific GI complaints – flatulence, recurrent abdominal pain, diarrhoea and/or constipation	Screening programmes in at-risk groups (those with a first-degree relative suffering from CD)
Loss of appetite	Malabsorptive symptoms – iron-deficiency anaemia, hypertransaminasaemia, Vit B12 deficiency, Vit D deficiency, folate deficiency, zinc deficiency	Retrospectively could be non-classic – if started on a gluten-free diet, improvement in quality of life
Abdominal distension	Fatigue	
Weight/muscle loss	Stomatitis	
Emotional changes	Alopecia	
Coeliac crisis	Arthralgia	
Intestinal intussusception	Rash – dermatitis herpetiformis	
	Fertility disorders	
	Idiopathic pulmonary haemosiderosis	
	Other	

** GI: gastrointestinal; Vit: vitamin; CD: coeliac disease*

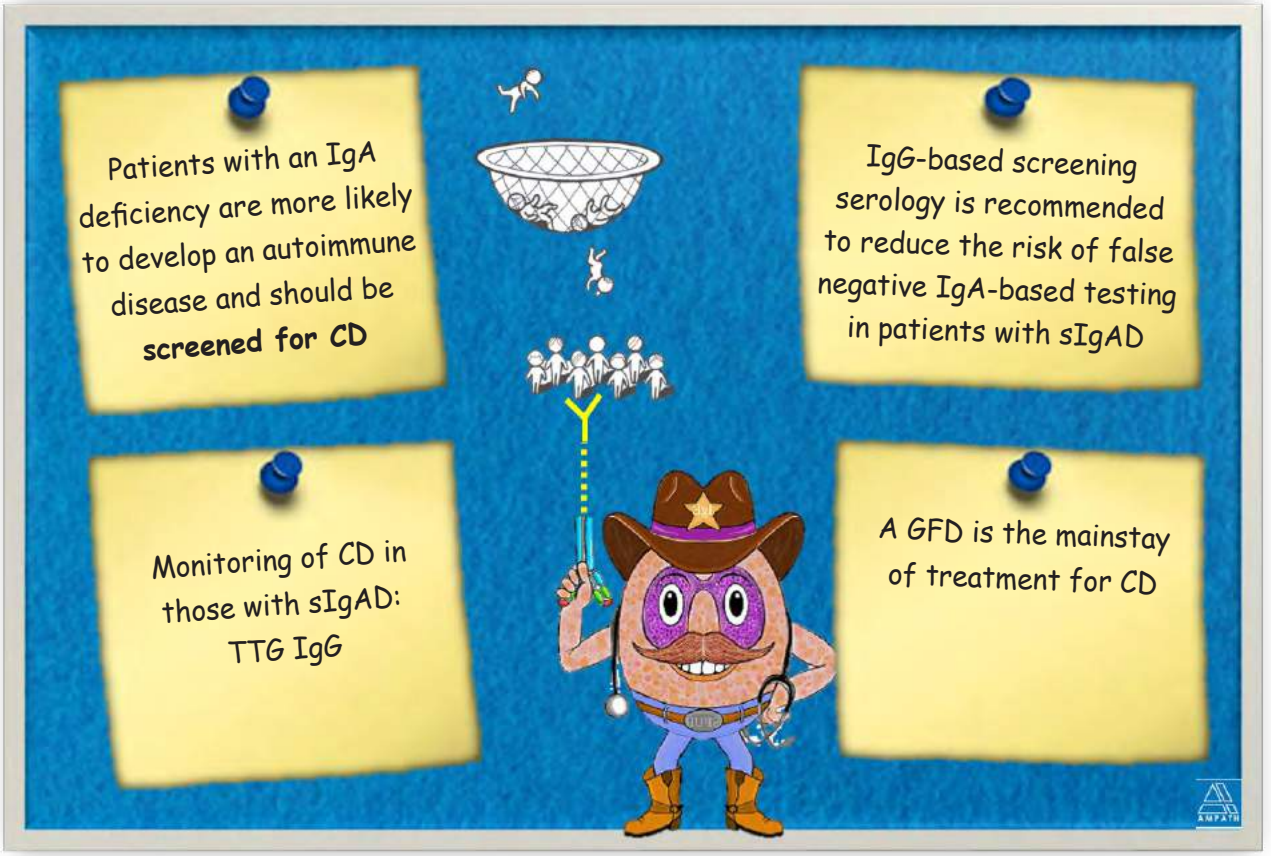
IgG against certain pathogens. Please select a product with minimal IgA, as anaphylactic reactions have been reported in patients with sIgAD.[4]

Be cautious about prescribing blood products in patients with sIgAD: these patients are at a risk of developing anaphylaxis.

With a strict adherence to her GFD, your patent's symptoms should improve within three months.[5,7] A repeat biopsy is recommended within 1–2 years to assess mucosal health and exclude secondary pathology, but this is at your discretion.

Warm regards
Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

The pain of the grain AND selective sIgAD can make you go insane: Autoimmune disorders and immunodeficiency disorders can go hand in hand; always exercise high level of suspicion.

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