DR SPUR'S MYSTERY CASE

will a spoonful of medicine help the sugar go down?

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Dr Mokete
General Practitioner

444 Deborah Avenue
Kathu
Northern Cape
0987

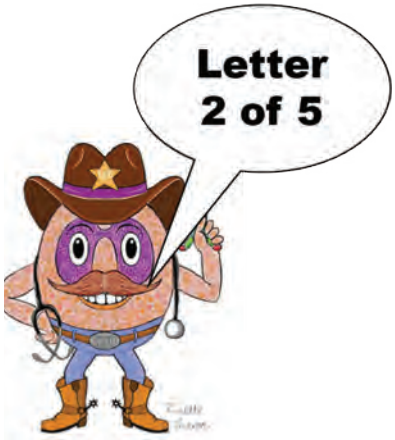
Tel: 053 956 5710

Dear Dr Spur

I am managing a 16-year-old suburban boy with insulin-dependent Type 1 diabetes in my practice. He was diagnosed at ten years of age when he presented with ketoacidosis and hyperglycaemia. His diabetes is difficult to control, possibly because he also has chronic abdominal pain and diarrhoea. *Giardia lamblia* PCR in the stool was positive twice in the past five months. He completed the prescribed treatment on both occasions, but the loose stools persist. I see chronic *Giardia lamblia* infection can be associated with immunosuppression, but my patient does not suffer from problematic respiratory infections. Should I be concerned about him?

Kind regards

Dr Mokete



Dear Dr Mokete

Recurrent or chronic infection with *Giardia lamblia* is certainly a red flag. While recurrent giardiasis may be associated with travel, daycare centre attendance, contaminated water and food sources, institutionalisation, and socio-economic deprivation, it is also one of the sentinel organisms associated with inborn errors of immunity (IEI).[1] It justifies investigations for primary immune defects. The associated Type 1 diabetes mellitus (DM) may also be a relevant finding. IEIs often involve endocrinopathies and primary immune deficiencies.

Primary immunodeficiency and autoimmune disorders were originally considered separate entities on opposite ends of the spectrum, but research has since revealed them to be underpinned by common mechanisms.[2] Dysregulation of the immune system can manifest with five cardinal components that include infections, autoimmunity, allergy, granulomatous inflammation and neoplasms. Non-infectious features may dominate or precede the clinical debut of problematic infections.

Type 1 DM results from autoimmune destruction of pancreatic β-cells by auto-reactive T- and B-lymphocytes. B-lymphocytes produce autoantibodies to β-cell antigens GAD65, IA-2, insulin and ZnT8, which are diagnostic.[3] There are three stages – all with positive islet autoantibodies. Glucose homeostasis is normal in stage 1. Glucose intolerance occurs in stage 2. Symptomatic diabetes manifests in stage 3 with classical symptoms such as polyuria, polydipsia, weight loss and ketoacidosis.

Your patient's laboratory results are summarised in Table I.

TABLE I: LABORATORY RESULTS FOR DR SPUR'S MYSTERY CASE

Test	Reference	Result 1	Result 2
Total protein	60–80 g/L	50 L	46 L
Albumin	40–55 g/L	40	–
Total Globulin gap	20–35 g/L	17 L	16 L
HbA1c	<5.6%	11.0 H	12.2 H
Anti-IA2	<0.02 IU/mL	340	–
Anti-GAD65	<0.02 IU/mL	>2 000	–
IgA	0.68–2.46 g/L	<0.06 L	0.09 L
IgM	0.46–2.42 g/L	0.50	0.47
IgG	7.57–16.21 g/L	3.8 L	2.1 L
IgE	0–100 IU/mL	12	–
Tetanus IgG	>0.1 IU/mL	0.15	1.5
H. influenzae IgG	>1.5 mg/mL	0.42 L	1.56
S. pneumo serotype PPS1	>1.3 µg/mL	0.35	0.51
S. pneumo serotype PPS3	>1.3 µg/mL	0.17	0.39
S. pneumo serotype PPS4	>1.3 µg/mL	0.15	<0.1
S. pneumo serotype PPS5	>1.3 µg/mL	0.42	0.65
S. pneumo serotype PPS6A	>1.3 µg/mL	0.26	0.19
S. pneumo serotype PPS6B	>1.3 µg/mL	0.15	1.6#
S. pneumo serotype PPS7F	>1.3 µg/mL	0.25	1.2
S. pneumo serotype PPS9V	>1.3 µg/mL	0.56	1.4#
S. pneumo serotype PPS14	>1.3 µg/mL	0.44	1.02
S. pneumo serotype PPS18C	>1.3 µg/mL	0.80	1.31#
S. pneumo serotype PPS19A	>1.3 µg/mL	0.72	1.54#
S. pneumo serotype PPS19F	>1.3 µg/mL	0.34	2.4#
S. pneumo serotype PPS23	>1.3 µg/mL	0.63	1.42#
% Protective serotypes	>70%	0%	46%
Total T-cells	1 000–2 200 cells/µL	1 200	–
CD4 T-cells	530–1 300 cells/µL	620	–
CD8 T-cells	330–920 cells/µL	580	–
Total B-cells	110–570 cells/µL	66 L	54 L
Total NK-cells	70–480 cells/µL	80	–
Memory B-cells	5.4–9.6%	2.3 L	2.8 L

TABLE II: ESID 2019 DIAGNOSTIC CRITERIA FOR CVID[4]

At least one of the following:
- increased susceptibility to infection
- autoimmune manifestations
- granulomatous disease
- unexplained polyclonal lymphoproliferation
- affected family member with antibody deficiency

AND a marked decrease of IgG and IgA either with or without low IgM levels (measured at least twice; <2 SD of the normal levels for their age)

AND at least one of the following:
- poor antibody response to vaccines (and/or absent isohemagglutinins), that is, an absence of protective levels despite vaccination where defined
- low switched memory B cells (<70% of age-related normal value)

AND secondary causes of hypogammaglobulinemia have been excluded (eg infection, protein loss, medication, malignancy)

AND diagnosis is established after the fourth year of life (but symptoms may be present before)

AND no evidence of profound T-cell deficiency, defined as two out of the following:
- CD4 numbers/microliter: 2–6 y <300, 6–12 y <250, >12 y <200
- % naive CD4: 2–6 y <25%, 6–16 y <20%, >16 y <10%
- T-cell proliferation absent.

It is important first to exclude secondary causes of immunosuppression such as infection, inflammation, protein-losing conditions, malnutrition, HIV infection, drugs and bone marrow disease. The serum total protein, albumin and immunoglobulins are useful screening tests for antibody deficiency. A low total protein and albumin value may indicate malnutrition or protein loss, while normal protein and albumin levels with a low globulin fraction may be a sensitive indicator of underlying immunodeficiency. Your patient presents with a persisting low globulin fraction.

An IgA and IgG deficiency was detected and confirmed with follow-up testing. He also has decreased B-cell and class-switched memory B-cell numbers, and impaired specific antibody production to recall antigens after vaccination. The findings are suggestive of common variable immunodeficiency (CVID). T-cell proliferation studies to mitogens should now be requested to exclude T-cell dysfunction and determine the risk of more severe infections.

The revised European Society for Immunodeficiency Disorders (ESID) diagnostic criteria for CVID are summarised in Table II.

Common variable immunodeficiency follows selective IgA deficiency as the second most prevalent IEI with immunodeficiency globally. It is a heterogeneous disorder that may manifest from childhood to the fourth decade of life with a wide clinical spectrum of pathology that includes susceptibility to viral, bacterial and fungal infections, autoimmunity, granulomatous inflammation, enteropathy, lymphoproliferative disease and malignancy.[2,5] Common malignancies in CVID are Hodgkin and non-Hodgkin lymphoma, leukaemia, astrocytoma, melanoma and sarcoma. Patients with dominating non-infectious presentations are often cared for by haematologists, rheumatologists, gastroenterologists or endocrinologists for some years before CVID diagnosis.

The key immunologic defects in CVID include faltering B-cell development, poor quantity and quality of antibody production, poor establishment of immune memory, T-cell activation defects and defects in immune tolerance. The central feature is hypogammaglobulinaemia with dominating mucopurulent sinopulmonary encapsulated bacterial infections (*Streptococcus pneumoniae*, *Haemophilus influenzae* Type B and *Moraxella catharralis*). Protracted Giardia lamblia diarrhoea is a common finding in CVID with undetectable IgA levels. Patients may also suffer from severe intracellular bacterial infections (such as *Mycoplasma pneumonia*) and *Ureaplasma urealyticum* arthritis.

An associated T-cell defect may deprive developing B-cells of essential T-cell co-stimulatory support and leave patients at risk of more severe infections, intracellular pathogens such as herpes simplex virus and listeria, and unusual and opportunistic pathogens such as mycobacteria, cryptosporidium, *Pneumocystic jirovecii* and fungi. It is essential to exclude a combined immunodeficiency when such infections occur.[2,6]

Several mechanisms lead to autoimmunity in CVID.[2,5] Thirty per cent of CVID patients develop autoimmune manifestations such as cytopaenia, inflammatory bowel disease,

autoimmune thyroid disease, Type1 DM, psoriasis, systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis or autoimmune encephalomyelitis.[7] Autoantibodies for organ-specific or systemic autoimmune disease should be routinely tested in IEI patients with suggestive clinical signs and symptoms. Conversely, a patient diagnosed with an autoimmune disease and suffering from unusual, persistent or recurrent infections should also be investigated for an IEI.

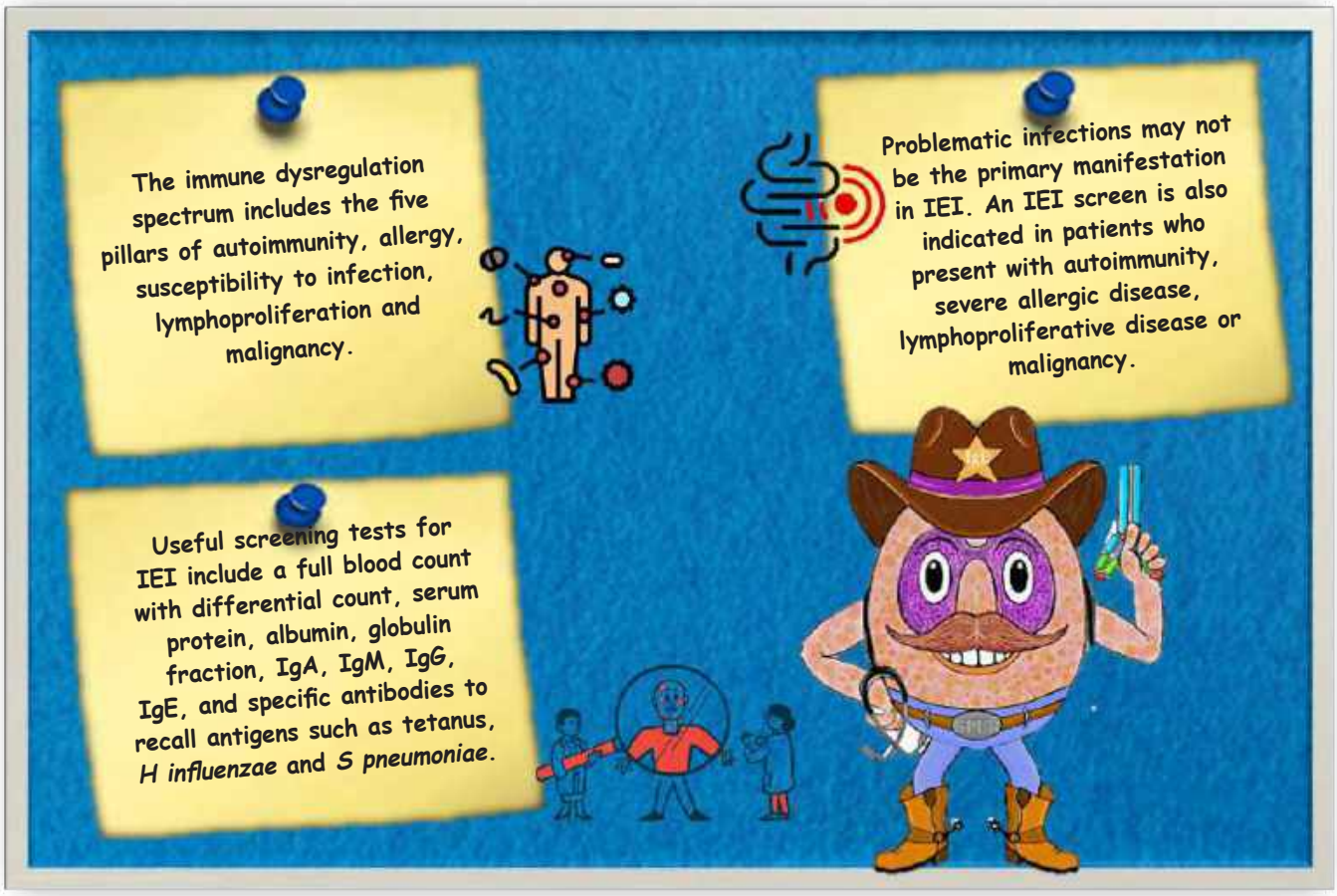
The genetic causes of CVID can be monogenic, polygenic, autosomal recessive or autosomal dominant with variable penetrance. High-throughput sequencing has identified a number of monogenic defects that impair B-cell activation and negative immune-cell selection. Genetic studies are not required to make a diagnosis but may identify a causative mutation in 20–30% of CVID patients.[5]

The general management of CVID includes vaccination, infection prevention, prompt treatment of infections, prophylactic antibiotics (eg azithromycin 5 mg/kg orally two or three times a week) and immunoglobulin replacement therapy (IRT).[2,5]

Autoimmune and auto-inflammatory manifestations are not addressed through IRT and require specific targeted therapy to preserve organ function and improve life expectancy. It is important not to neglect the non-infectious manifestations since they contribute greatly to morbidity and mortality.

We now know that your patient's Type 1 DM and recurrent *Giardia lamblia* infections fit in with two of the five pillars of the immune dysregulation spectrum. The autoimmune diagnosis preceded the infectious diagnosis by six years. Valuable time to preserve organ function may be lost on the road to final diagnosis. It is good to keep the five pillars of immune dysregulation in mind and to seek the missing components in patients presenting with one of the pillars. To complete the five-pillar assessment, your patient should also be assessed for problematic allergic disease, other autoimmune diseases, lymphoproliferative disease and malignancy. A causative IEI mutation-targeted genetic panel testing will be useful for family screening. T-cell functional assessment is recommended to assess the risk of future severe or sentinel infections that may require long-term prophylactic antibiotics.

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:
CVID diagnosed in a patient with type 1 diabetes. Medicine for that WILL help the sugar go down.

AUTHORS
Lizelle Nagel[2], Sylvia van den Berg[1,2], André van Niekerk[2]
1 Department of Immunology, Ampath Laboratories, South Africa
2 Department of Paediatrics and Child Health, Steve Biko Academic Hospital, University of Pretoria, South Africa

ILLUSTRATORS:
Rinette Theron, Marlene Buitendach

REFERENCES:

1. Cohn IS, Henrickson SE, Striepen B, Hunter CA. Immunity to Cryptosporidium: Lessons from Acquired and Primary Immunodeficiencies. J Immunol. 2022;209(12):2261–2268. https://doi.org/10.4049/jimmunol.2200512.
2. Amaya-Uribe L, Rojas M, Azizi G, Anaya JM, Gershwin ME. Primary immunodeficiency and autoimmunity: A comprehensive review. J Autoimmun. 2019;99:52–72. https://doi.org/10.1016/j.jaut.2019.01.011.
3. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic Type1 diabetes: A scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015;38(10):1964–1974. https://doi.org/10.2337/dc15-1419.
4. ESID Registry. Working definitions for clinical diagnosis of PID. Available from: https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria.
5. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Ann Allergy Asthma Immunol. 2019;123(5):454–460. https://doi.org/10.1016/j.anai.2019.07.014.
6. Wong GK, Huissoon AP. T-cell abnormalities in common variable immunodeficiency: The hidden defect. J Clin Pathol. 2016;69(8):672–676. https://doi.org/10.1136/jclinpath-2015-203351.
7. Mohammadi F, Yadegar A, Mardani M, et al. Organ-based clues for diagnosis of inborn errors of immunity: A practical guide for clinicians. Immun Inflamm Dis. 2023;11(4):e833. https://doi.org/10.1002/iid3.833.