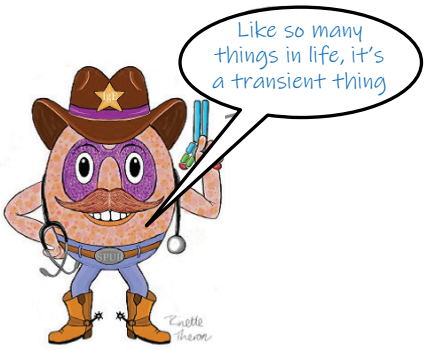


DR SPUR'S MYSTERY CASE

The mystery case of transience

Welcome to Dr Spur's Immunology Clinic

Referral letter:

General practitioner
Bela-Bela
Dr AJ Theron

Dear Dr Spur
I am treating a 12-month-old boy, who has had three episodes of otitis media in the past six months, after which a tympanostomy was performed. This boy also had two incidents of bronchitis (microbial studies not performed) and RSV bronchiolitis. He had one incident of suppurative conjunctivitis. He always has a runny nose and has mild eczema. Cow's milk allergy was demonstrated. He is otherwise growing well and a happy, playful child. He is attending a crèche half-day with 15 children in his class. He has two older siblings; a four-year-old sister and a three-year-old brother, who are both attending a preschool. His vaccinations are up to date. His mom said she suspected that there may be something wrong with her son's immune system and I subsequently ordered immunoglobulin levels and a full blood count (FBC). His IgA level was slightly decreased (IgA = 0.19 g/L), his IgM was normal and an IgG level of 3.2 g/L (decreased for his age) was reported. He was slightly neutropaenic. Can you please evaluate him and advise on further management? The mother is deeply concerned about these findings.

Kind regards
Dr AJ Theron

Dear Dr Theron

Thank you for the referral of this delightful little boy. He seems well and is at the 90th percentile for height and weight. The mom gives a clear history of this boy being healthy in between the episodes of infection. There is no family history of immune deficiency.

I reassured her and told her that we have to do a couple of investigations to exclude a more severe immunodeficiency, but he might very well have transient hypogammaglobulinaemia of infancy (THI).

I ordered repeat IgA, IgM and IgG testing to exclude a transient decrease. I also requested IgE levels. The IgA level was still slightly decreased (0.18 g/L) with IgG levels at 3.01 g/L (2 SD below reference range for his age group). His IgE level was slightly raised (100 IU/mL). I also requested his vaccine-specific antibodies to evaluate his response to his previous vaccinations. He had protective tetanus antibody levels (2.3 IU/mL), slightly decreased *H influenzae* antibodies (0.75 mg/L) and he demonstrated protective antibody titres (> 0.3 ug/L) to 60% of the *S pneumoniae* serotypes tested, which are acceptable in this age group. On his FBC, the neutrophil count normalised. His T-lymphocyte numbers demonstrated a mild decrease in CD4 and CD8 counts, 850 cells/uL and 620 cells/uL respectively, with normal B- and NK-cell numbers. The slightly decreased T-lymphocytes are most likely secondary to his recent episode of bronchitis. These are important findings, because normal B-lymphocyte numbers exclude a diagnosis of XLA in a boy, and a severe T-cell defect will be most unlikely with T-cells being well represented. X-linked conditions should always be considered in boys. CD40-Ligand (CD40L) expression was evaluated to exclude X-linked hyper-IgM syndrome (which can present with low IgA and IgG levels and elevated or normal IgM levels). CD40 Ligand was present on T-cells and X-linked hyper IgM therefore probably excluded (good vaccine responses are also against a diagnosis of hyper-IgM syndrome). If a diagnosis of hyper-IgM syndrome was clinically considered, genetic testing for the CD40L gene could have been pursued, as CD40L expression doesn't exclude a mutation with a functional defect. Autosomal recessive types of Hyper-IgM syndrome could also have been considered if there were additional clinical indicators. The boy did not have any signs of a syndromic PID, including Di George.

Transient hypogammaglobulinaemia of infancy (THI) is a primary immunodeficiency caused by a transient drop of IgG levels in an infant, beginning between five and 24 months of age.

IgG is produced at low levels by the foetus, and it is the only immunoglobulin to cross the placenta. At birth, IgG levels are equivalent to that of the mother. The infant starts producing their own IgG and this gradually increases to the expected levels by six months of age. The process of own IgG production overlaps with the declining maternal IgG levels. A physiologic nadir in IgG is expected between three to six months of age, when maternal levels are at their lowest. This represents physiologic hypogammaglobulinaemia and is mostly not clinically significant. Premature babies have less maternal IgG

antibodies and reach the physiologic nadir sooner.

In cases of THI, the physiologic hypogammaglobulinaemia is prolonged and extends beyond six months of age. The IgG levels remain significantly lower at two standard deviations below the normal for age-matched controls. IgA and IgM may or may not be decreased.

Immunodeficiencies such as common variable immunodeficiency cannot be excluded until the transient period is over and IgG levels return to normal. The diagnosis of common variable immunodeficiency (CVID) is then made retrospectively. In patients with CVID, immunoglobulins remain low and vaccine responsiveness does not normalise.

Patients may suffer upper and lower respiratory tract infections. Approximately 30 to 50 per cent of THI patients have allergic disorders, including food allergies. More severe manifestations include urinary tract infections, gastroenteritis, invasive infections and even prolonged oral thrush.

Some infants with THI are asymptomatic, and the diagnosis could be made after an immune evaluation due to a family history of PID, the incidental finding of a low globulin gap or other reasons for an immune workup.

Most infants with THI produce normal or near-normal antibodies to infections or protein vaccines, including diphtheria, tetanus, hepatitis A and B, conjugated *Haemophilus influenzae* type B, measles, mumps and rubella vaccines. Antibodies to polysaccharide antigens also are mostly within range if tested after the age of two years (after Pneumovax vaccine challenge). A subset of patients with insufficient vaccine responsiveness may also normalise with the resolution of THI. Tetanus toxoid vaccine is highly immunogenic and, if an infant fails to respond to this vaccine, a more severe immunodeficiency should be sought. Occasionally, infants with THI may also have a transient neutropaenia.

Lymphocyte subsets, including memory and class-switched B cells as well as T-cell functional assays are mostly normal. It is important to request lymphocyte subsets, as a decreased B-cell number should prompt further investigation to exclude X-linked agammaglobulinaemia or more severe humoral immunodeficiencies. Patients with a severe combined immunodeficiency will usually present with very low lymphocyte counts, severe and recurrent viral or fungal infections, and failure to thrive.

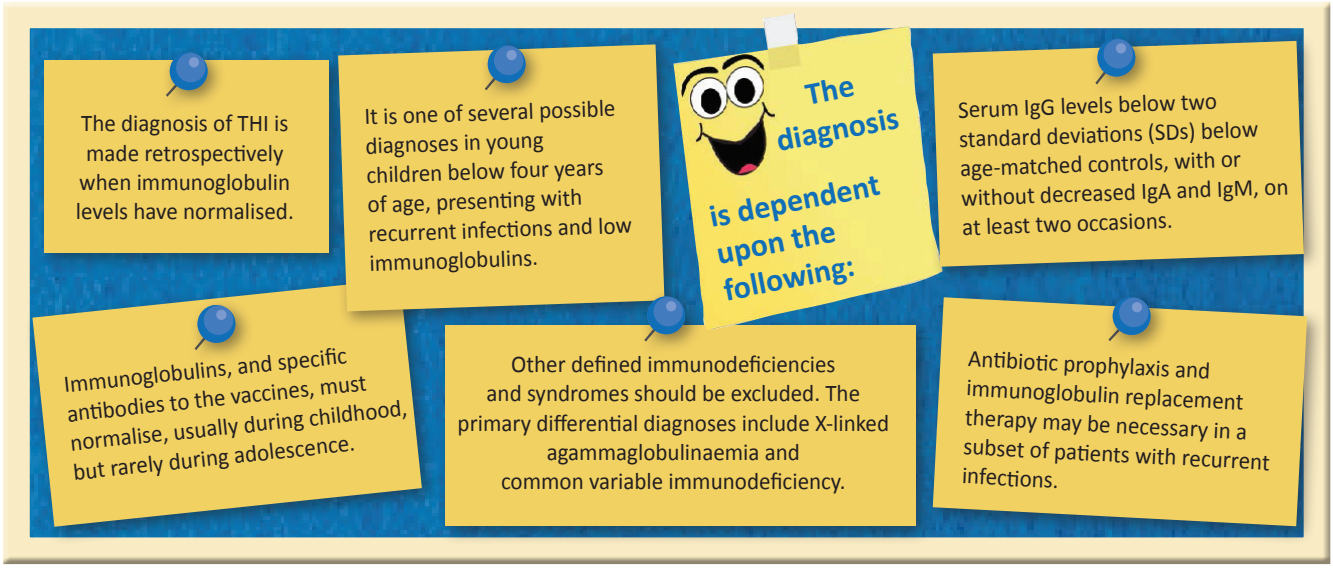
Close follow-up and observation is appropriate for most patients, with treatment for infections as needed. Antibiotic prophylaxis should be considered for patients with recurrent respiratory and/or ear infections. Sometimes, antibiotic prophylaxis is reserved for winter months in a child that doesn't suffer from as many infections. Patients with recurrent otitis media often benefit from tympanostomy.

Immunoglobulin replacement therapy (IRT) should be considered for patients with THI who have recurrent, severe infections, despite antibiotic prophylaxis. They are usually treated with IRT for short periods of time, ranging from a single injection to up to 18 months of therapy. These children should be followed up six-monthly (or as clinically dictated), until a complete clinical and laboratory resolution is achieved and sustained. Based on frequency and severity of infections, IRT should be discontinued when the child is clinically stable and re-evaluated after six months.

It is usually recommended that these children be cared for at home until they have outgrown THI. If not possible or practical, they should ideally attend a school with small classes.

Infections and immunoglobulin levels resolve in most patients by two to four years of age and a retrospective diagnosis should be made. Rarely, resolution can be observed only beyond the first decade of life. All cases of THI must resolve, if not, another diagnosis should be considered.

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

'A probable case of Transient Hypogammaglobulinaemia of Infancy (THI). The diagnosis can be confirmed only after four years of age, or even older.'

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CPD QUESTIONNAIRE

Earn 3 CPD points after you have read the journal by completing the following questionnaire online on the Cipla DNA Academy site www.cipladnaacademy.co.za. In order to get your points you need to be registered on the Cipla DNA Academy and log in directly at www.cipladnaacademy.co.za or follow the link from the ALLSA website member section. There is only one correct answer and you will have only two opportunities to submit the questionnaire, so please check your answers carefully. A pass of 70% or higher is required to gain 3 points. This CPD activity is for paid up ALLSA members only.

ETHICS: NEW ETHICAL GUIDELINES ON SOCIAL MEDIA FOR HEALTH CARE PROFESSIONALS

1. *True or false:* Healthcare professionals must obtain the written consent of a patient before publishing any information in media or on platforms to which the public has access, even if such information does not contain any identifiable data.
2. *True or false:* Patient information received via social media does not need to be treated as confidential.
3. *True or false:* If health or medical advice is shared via social media, it should be evidence-based, scientifically sound and it should be generic.
4. *Choose the correct answer:* According to Section 14 of the National Health Act, a healthcare professional may only disclose a patient's information:
   a. With the patient's consent, through a court order or if non-disclosure will result in serious harm to the public health.
   b. When the patient has died.
   c. When instructed to do so by an employer, e.g. National Department of Health.
   d. All of the above.
5. *Choose the correct statement:* When healthcare professionals see unprofessional content posted on social media by colleagues they must:
   a. draw the attention of the colleague to that content, with the suggestion that he remove it;
   b. post a message on social media denouncing the unprofessional content;
   c. report the colleague to the HPCSA without engaging with him;
   d. remove the colleague from their social media contacts.

THE VALUE (OR OTHERWISE) OF SOCIAL MEDIA TO THE MEDICAL PROFESSIONAL: SOME PERSONAL REFLECTIONS

6. *Choose the INCORRECT statement:* The "Nutrition Trial of the Century"
   a. established that providing medical information on social media creates a legal doctor-patient relationship.
   b. established that the prescription of a high-fat (ketogenic) diet for infant weaning is neither "unconventional" nor "not evidence-based".
   c. was spread over three years (in "court").
   d. showed that providing scientifically-based and correct information on social media (Twitter) will not necessarily protect a medical practitioner from the possibility of prosecution (if reported to the HPCSA).
   e. None of these statements is incorrect.
7. *Choose the INCORRECT statement:* Medical practitioners active on social media need to be aware that
   a. medical advice should not be given to specific individuals on any social media platform.