DR SPUR'S MYSTERY CASE

The case of the chicken or is it the egg?

Welcome to Dr Spur's Immunology Clinic
Referral letter:

Springbok Family practice

Dr Abel Deville
General Practitioner

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Tel: 027 981 4000

Dear Dr Spur

Re: Advice on recurrent airway infections in a three-year-old patient
I am writing to ask your advice on Michael, a three-year-old patient, whose mother is concerned about the possibility of an underlying immune deficiency. She reports that he is frequently unwell, presenting with airway infections almost every month since she discontinued breastfeeding him at nine months so that she could return to work. He started attending daycare at that point.

Clinical history
Michael's primary symptoms include a recurrent runny nose associated with an irritating cough. It worsens at night and with physical activity. Each episode of cough lasts about three weeks, subsiding for only one to two weeks before recurring. Despite this pattern, Michael has been gaining weight appropriately, has no history of exposure to tuberculosis or HIV, and has received all vaccinations according to the EPI schedule.

Investigations to date
To rule out common causes of recurrent infections, I have undertaken the following investigations:
- Immunoglobulin levels (IgG, IgA, IgM): Slightly decreased IgG and IgA levels.
- Total IgE level: Slightly elevated.
- Allergy tests for inhaled allergens (specific IgE): Negative.
- Sweat chloride test: Normal.

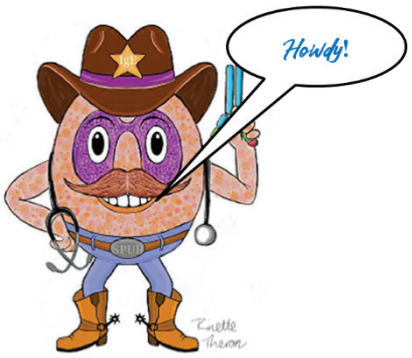
Management to date
Following our standard practice, my partners and I have managed his episodes with antibiotics and short courses of prednisolone to mitigate the duration of symptoms and prevent complications. Despite these interventions, the recurrent nature of his illness persists.

Parental concerns
Michael's mother remains convinced that an immune deficiency might be the underlying issue. Her concern stems from the frequency of his illnesses and the recurring nature of his symptoms.

Request for guidance
I would greatly appreciate your expert opinion on the following:
- Could Michael's recurrent symptoms still indicate an underlying immune deficiency?
- Are there additional investigations or referrals that you would recommend at this stage?
- Could there be an alternative diagnosis or contributing factors, such as environmental or anatomical issues, that we should consider?

Thank you for your time and expertise in this matter. I look forward to your guidance on the best course of action for Michael.

Best regards,
Dr Abel Deville



Dear Dr Abel

This patient presents a diagnostic challenge due to the potential overlap between corticosteroid-induced secondary immunodeficiency and a primary immunodeficiency disorder. Repeated short courses of oral corticosteroid treatment can have cumulative effects on the immune system, even when taken intermittently. These medications suppress the immune response by reducing inflammation and dampening the activity of immune cells, such as T-cells and macrophages. Short courses and frequent use may lead to an increased risk of infections, impaired wound healing and a potential disruption of normal immune regulation. In addition, repeated exposure to corticosteroids may suppress the hypothalamic–pituitary–adrenal (HPA) axis, which could further affect the body's ability to mount an adequate stress or immune response when needed.

However, the observed immune cell deficiencies also raise the possibility of a primary immunodeficiency, such as Common Variable Immunodeficiency (CVID) or another combined immunodeficiency. Primary immunodeficiencies often present with recurrent infections and immune dysregulation, which could explain the patient's clinical history.

Key dilemma: distinguishing between the possibility of either secondary or primary immunodeficiency

1. **Secondary Immunodeficiency** (SID) due to repeated short courses of corticosteroid use, which can suppress immune function and lead to increased susceptibility to infection.
2. **Primary Immunodeficiency** (PID) due to an intrinsic defect in the immune system, possibly explaining both the patient's recurrent infections and abnormal immune markers.

Further testing is required to better define the nature of this immune dysfunction.

Next steps and management

Given the patient's ongoing symptoms and the abnormal immune findings, I would recommend the following:

- **Limit systemic corticosteroid use:** A careful plan to prescribe systemic corticosteroids only when correctly indicated and reduce their use should be initiated. Corticosteroids can suppress lymphocyte numbers and function transiently for up to 60 days and may impair vaccine responsiveness.
- **Additional immunological testing:** This includes testing for specific antibody responses to vaccines and further flow cytometry to assess T-cell function and maturation. These investigations should ideally be done after 2–3 months of the discontinuation of corticosteroids.
- **Consideration of primary immunodeficiency:** Genetic testing may then be considered to diagnose specific PIDs such as CVID or combined immunodeficiencies.

This case underscores the need for a thorough workup to differentiate between SID due to corticosteroids and a PID disorder. Environmental factors and anatomical abnormalities should also be considered. Correctly identifying the underlying cause is crucial to managing the patient's symptoms and preventing further complications.

SIDs remain the most common cause of immune dysfunction. These include factors such as immunosuppressive medication, malignancies, protein-losing conditions and malnutrition.

Secondary immunodeficiencies in children with a focus on corticosteroids

In the era of immune-modulating biologics and immunosuppressive medications, distinguishing between primary and secondary antibody deficiencies is critically important. In the clinical setting, unravelling the complex relationship between PIDs and SIDs can be particularly challenging.

SIDs are acquired impairments in immune cell counts and/or function. They are the result of external factors rather than congenital defects. These deficiencies result from infections, malnutrition or chronic diseases or medications. Unlike PIDs, which stem from genetic abnormalities, SIDs are reversible by treating the underlying cause. Among the many factors contributing to SIDs, corticosteroids are a notable cause due to their widespread use in medicine.

Pathophysiology of secondary immunodeficiency

The efficacy of the immune system can be compromised by external agents that affect its components, including T and B lymphocytes, phagocytes or the complement system. In children, common causes of SID include severe infections (eg, HIV, tuberculosis), protein-losing conditions, malnutrition, chemotherapy and immunosuppressive drugs. The degree and type of immune suppression depends on the causative factor.

Corticosteroids, widely used for their anti-inflammatory and immunosuppressive properties, can affect immune function significantly. While they are essential in managing conditions such as asthma, autoimmune diseases and organ transplant rejection, their use suppresses various immune pathways.

Corticosteroids as a cause of secondary immunodeficiency

Corticosteroids such as prednisone and dexamethasone exert their effects by modulating gene expression, reducing inflammation and inhibiting immune responses. Their immunosuppressive effects can occur in the following ways:

1. **T-cell suppression:** Corticosteroids inhibit T-cell activation and proliferation, reducing the ability of the immune system to respond to infections effectively.
2. **Phagocyte function impairment:** These drugs impair the recruitment and function of neutrophils and macrophages, which are crucial to pathogen clearance.
3. **Antibody production:** Corticosteroids suppress B-cell activity and antibody synthesis, further weakening the adaptive immune response. It has been shown that even low-dose corticosteroid therapy may lead to the extended suppression of humoral immunity, only to resolve over time – which may take as long as two years.

In children, the regular use of corticosteroids can lead to heightened susceptibility to infections, delayed wound healing and the reactivation of latent infections, such as tuberculosis or herpesviruses. Even short courses of corticosteroids can increase the risk of infection transiently, particularly in immunocompromised children.

Clinical implications and management

For paediatric patients on corticosteroid therapy careful risk–benefit analysis is crucial. Strategies to mitigate immunosuppression include these:

- **Administer only when absolutely necessary.** The injudicious use of systemic corticosteroids is strongly discouraged. Whenever possible, topical corticosteroids, instead of systemic corticosteroids, should rather be used if corticosteroid therapy is indicated.
- **Tapering dosages:** Use the lowest effective dose for the shortest duration possible if clinically indicated. The safe tapering of corticosteroid doses (after longer-duration use) involves gradually reducing the dosage under medical supervision to prevent withdrawal symptoms and adrenal insufficiency.
- **Infection monitoring:** Close surveillance for early signs of infection is vital.
- **Preventive measures:** Vaccination against common pathogens and prophylactic antimicrobials may be considered in specific cases.
- A**djunct therapies:** Alternatives or adjunct treatments, such as biologics with less broad immunosuppressive effects, should be explored whenever feasible.

Other factors that may contribute to his symptoms include early crèche attendance and potential environmental influences.

Early crèche attendance

These factors should be considered in the case of young children attending a crèche:

1. **Increased exposure to pathogens:** Children in crèches are often exposed to a higher density of other children, leading to increased contact with viruses and bacteria. This contributes to more frequent upper respiratory tract infections (URTIs).
2. **Immature immune system:** Young children have developing immune systems, which may not effectively combat the range of pathogens they encounter in group settings, leading to recurrent minor illnesses.
3. **Adaptation over time:** While infections are more frequent initially, this exposure can help to 'train' the immune system, possibly reducing the frequency of illness as the child grows older.

Environmental factors

These environmental factors should be considered in the case of young children attending a crèche:

1. **Indoor air quality**: Poor ventilation, exposure to secondhand smoke and allergens (eg, dust, pet dander) can irritate the respiratory system, exacerbating cough and respiratory infections.
2. **Seasonal variations:** Changes in the weather, especially during colder months, can increase the prevalence of viral infections.
3. **Socioeconomic status:** Nutrition, living conditions and access to healthcare can also influence a child's susceptibility to infections. Crowded living spaces, for instance, can lead to higher rates of transmission.
4. **Hygiene practices:** Inadequate hygiene or shared toys and surfaces at crèches can promote the spread of infectious agents.

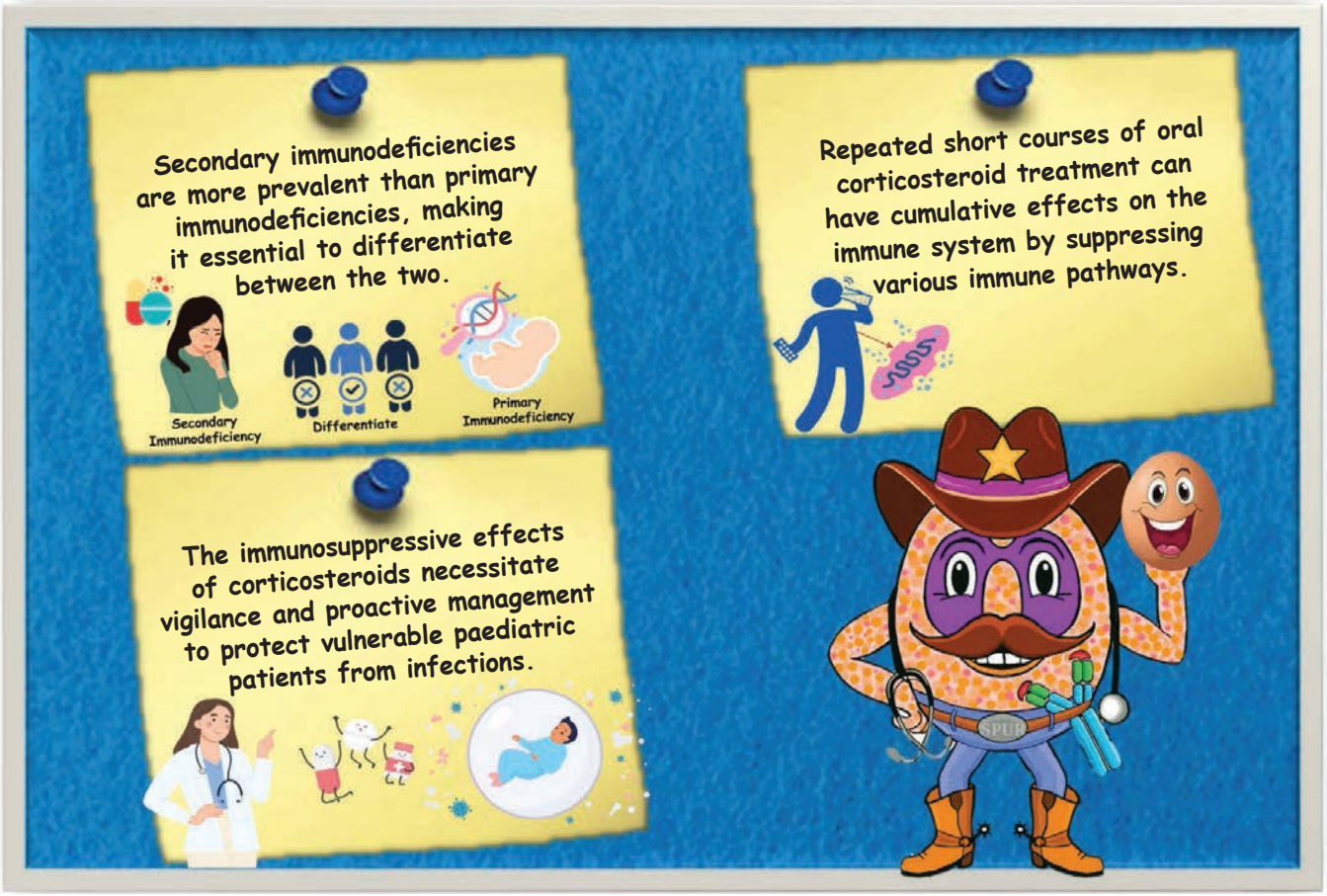
Although recurrent minor infections and coughs are common in children who attend crèches, they are typically self-limiting and become less frequent as immunity strengthens with age. Responding appropriately to environmental factors, such as maintaining good hygiene and improving air quality, can mitigate some risks.

Conclusion

The cause of the recurrent infections is likely multifactorial, with crèche attendance and environmental factors contributing. Anatomical abnormalities should be ruled out. Regular intermittent use of short course corticosteroids may impair his immune system and could also explain the abnormal immunology results. Therefore, these investigations should be conducted after discontinuing corticosteroids for at least 2–3 months.

Both PIDs and SIDs can manifest in the form of infections, immune dysregulation, autoimmune conditions, lymphoproliferation and malignancies. Distinguishing between these conditions in the clinical setting can often be complex and challenging. SIDs in children, particularly those induced by corticosteroids, highlight the delicate balance required in paediatric care. While corticosteroid immune suppression plays an important role in managing various diseases, their immunosuppressive effects necessitate vigilance and proactive management to protect vulnerable paediatric patients from infections. Awareness and judicious use of these drugs can help to mitigate their risks while maximising the therapeutic benefits.

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

Dr Spur's mystery case solved: It's the egg!

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