A 2-year-old girl with frequent infections

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A 2-year-old girl has experienced frequent infections from early infancy, including repeated chest infections, UTIs and ear infections. She developed asthma at age 13 months and has needed oral prednisolone on several occasions. What further tests does the patient need and what can be done to prevent her repeated chest infections?

Case scenario

Lilly, now aged 2 years, has had frequent respiratory and urinary tract infections (UTIs) for most of her life. At 5 weeks of age, she was hospitalised with bronchiolitis. Between 3 and 5 months of age, she was frequently taken to her GP with repeated chest infections. Between 6 and 9 months of age, she had multiple UTIs and was given trimethoprim prophylaxis. Subsequent kidney function tests showed no structural abnormalities, and she was taken off the prophylaxis. At 10 months of age, she was hospitalised with gastroenteritis and needed IV rehydration. At 13 months of age, three courses of antibiotics failed to clear a chest infection, resulting in her being hospitalised with pneumonia. Following this, she developed asthmatic symptoms and was prescribed an inhaled corticosteroid (beclometasone 100 mcg twice daily) plus salbutamol as needed. An isolated immunoglobulin A (IgA) deficiency test was positive.

Further recurrent UTIs occurred at 15 months of age and trimethoprim prophylaxis was reinstated but changed to nitrofurantoin at 19 months of age. At 20 months of age, her asthmatic symptoms worsened and she was prescribed a course of oral prednisolone.

Lilly is currently taken to her GP or hospital once or twice weekly because of her asthmatic episodes, and has needed oral prednisolone on four separate occasions. The recurrent chest infections also continue plus the occasional ear infection.

What further tests are needed for this patient and what can be done to prevent the repeated chest infections?

Commentary

Infections are common in otherwise healthy young children with normal immune systems. These children may have more than 10 viral respiratory tract infections (RTIs) a year, particularly when in frequent contact with other children, such as at child care.

Although frequent infections can worry parents, most children do not have a problem with their immune function. However, it is important to identify children with immune deficiency early so appropriate treatment can be initiated with the aim of minimising infections and subsequent end organ damage, such as bronchiectasis.

Lilly has experienced frequent infections from early infancy and has some features that indicate possible immune deficiency. Primary immunodeficiency disorders (PIDDs) are inborn errors of immunity that result in a predisposition to infection. In many

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1. 10 WARNING SIGNS OF PRIMARY IMMUNODEFICIENCY IN CHILDREN*

Although not exhaustive, the following signs in a child should prompt consideration of immune functioning testing and/or referral to a paediatric immunologist for evaluation:

- four or more ear infections within one year
- two or more severe sinus infections within one year
- two or more months of treatment with antibiotics with little effect
- two or more episodes of pneumonia within one year
- failure of an infant to gain weight or grow normally
- recurrent deep skin or organ abscesses
- persistent thrush in mouth or fungal infection on skin
- need for intravenous antibiotics to clear infections
- two or more deep-seated infections, including septicaemia
- family history of primary immunodeficiency.

*These warning signs were developed by the Jeffrey Modell Foundation (www.info4pi.org). Consultation with primary immunodeficiency experts is strongly suggested.

cases PIDDs are associated with other features of immune dysfunction, such as excessive inflammation, autoimmunity or a predisposition to malignancy. Although individually rare, more than 300 distinct PIDDs have been described.[1] PIDDs are inherited and therefore distinct from secondary causes of immunodeficiency, such as immunosuppressive medications, HIV infection and malnutrition, which should also be considered.

The classification of PIDDs is increasingly complex and beyond the scope of this discussion. However, in general, causative pathogens and patterns of infection help guide investigations; for example, children with antibody deficiency commonly present with sinopulmonary infections.

Identifying possible immune deficiency

Consideration of the points below may help determine whether Lilly or another child with possible immune deficiency might benefit from immune evaluation and possible referral to a paediatric immunologist.

- When assessing a child with frequent infections, clinical features of concern would be the need for multiple courses of antibiotics to clear an infection, progression despite appropriate oral antibiotics, a frequent need for IV antibiotics, a chronic wet cough or acute otitis media with perforation or chronic purulent aural discharge. Although many children with normal immune systems will exhibit these features with some infections, often due to a more virulent pathogen, repeated presentations with these signs should prompt consideration of immune deficiency (Box 1).
- Is Lilly growing appropriately? A pattern of faltering growth may result from frequent, severe or persistent infections, or be associated with excessive inflammation.
- It would be helpful for Lilly's GP to define her respiratory exacerbations and assess for identifiable infections. Are Lilly's symptoms caused by infection, and if so can the pathogen be identified? Are her chest infections recurrent lower RTIs with chest x-ray changes or viral upper RTIs with identifiable viruses? Although most children with coryzal symptoms only need supportive care, nasal viral swabs can provide useful information in a child presenting frequently with respiratory symptoms.
- It is helpful to confirm the presence of a causative organism and determine if Lilly is able to clear viral infections, because a failure to clear viral infections is concerning for an immune defect. Depending on the virus and site of infection, prolonged viral carriage may present with chronic respiratory symptoms or chronic diarrhoea.
- Does Lilly have an opportunistic infection, such as chronic thrush due to *Candida* sp?
- In addition to frequent identifiable infections, does Lilly have other signs of immune dysfunction, such as autoimmune phenomena (idiopathic thrombocytopenia or autoimmune haemolytic anaemia), inflammatory conditions (inflammatory bowel disease) or severe eczema? A PIDD is more likely if one of these conditions is present in association with frequent infections.
- When Lilly is well, does she have interval symptoms, such as a chronic productive cough, or does she only have symptoms with discrete infections? Persistent symptoms may suggest permanent organ damage as a result of frequent or chronic infections, such as bronchiectasis presenting with a chronic moist cough.
- Are Lilly's parents related? Parental consanguinity increases the risk of autosomal recessive PIDDs.
- Does Lilly have a family history of frequent infections or deaths in childhood?

Specific points about Lilly's history

Lilly has had recurrent respiratory infections from early infancy, at times requiring multiple courses of oral or IV antibiotics to clear. She also appeared to have a reduction in chest infections while on antibiotic prophylaxis for UTIs. Transplacentally acquired maternal antibody (IgG) wanes during the first six months of life. If an infant's own antibody production is impaired, the resulting hypogammaglobulinaemia may predispose to bacterial infections from 4 months of age.

Lilly has also had ear infections and it would be important to know if she had associated tympanic membrane perforation

or chronic purulent aural discharge.

Respiratory symptoms may also be caused by reactive airways, which can complicate and prolong benign viral infections but are not a sign of immunodeficiency. It is possible Lilly has undertreated reactive airways causing frequent exacerbations that may mimic infection.

Isolated IgA testing is not helpful, except to aid in the interpretation of IgA-based testing such as coeliac serology, as IgA may mature slowly and adult levels may not be reached until school age. In addition, many people with isolated IgA deficiency do not experience an increased frequency of infections. However, a low IgA in a patient with frequent proven sinopulmonary infections should prompt assessment of IgG and IgM levels.

Although UTIs are not a feature of immunodeficiency, structural abnormalities of the urinary tract, such as vesicoureteric reflux, may also be associated with an excessive number of infections, as can structural abnormalities at other sites, such as midface hypoplasia. Structural abnormalities usually only cause recurrent infections at one site only.

Management

Features to consider on physical examination for a patient such as Lilly are listed in Box 2. Initial investigations to consider for Lilly in primary practice are:

- chest x-ray: consider acutely if Lilly has signs of a lower RTI or when well to assess for evidence of chronic lung changes
- nasopharyngeal aspirate or throat swab (viral and bacterial) to assess for causative organisms
- full blood count to assess for white cell count and differential, platelet count (thrombocytosis may suggest inflammation and thrombocytopenia possibly ITP) and haemoglobin, which may be reduced in chronic disease
- immunoglobulins (IgG, IgA and IgM) provide a quantitative assessment of humoral immunity
- lymphocyte subsets to assess T and B cell numbers, essential cells of adaptive immunity.

Referrals to consider

Given the frequency of Lilly's as yet undefined respiratory presentations, referral to a respiratory physician could be useful as her symptoms may be from undertreated asthma, chronic suppurative lung disease or recurrent infections. Review by a paediatric immunologist may be helpful as there are red flags for immunodeficiency, and should be initiated if there is significant parental or practitioner concern.

In addition to the initial primary care investigations listed above, a paediatric immunologist may consider:

- vaccine immunoglobulin responses – a measure of antibody function
- chest CT – to assess for bronchiectasis
- genetic testing – often required for diagnosis of PIDDs as functional assessment of the immune system can be limited.

Conclusion

PIDDs are rare but important not to miss because early directed treatment will significantly reduce morbidity and mortality. Immunodeficiency should be considered in children who have unusual presentations or outcomes from infection, in children with persisting infections and in those with end organ damage. Autoimmune and inflammatory conditions, or poor growth in a child with frequent, unusual or severe infections should also prompt consideration of a PIDD. MT

2. PRIMARY IMMUNODEFICIENCY PHYSICAL EXAMINATION FINDINGS

Given the heterogeneity of primary immunodeficiency disorders, it is not possible to list all potential concerning physical examination findings. However, points that may be helpful in Lilly's case include the following.

- Dysmorphism: is Lilly dysmorphic? Immunodeficiency is recognised in a number of genetic syndromes, such as 22q11 deletion syndrome
- Nutrition: is Lilly growing well? Assess height, weight and pattern of growth using centile charts
- Respiratory symptoms: Lilly needs a thorough respiratory examination to assess for signs of suppurative lung disease, such as clubbing, crepitations and evidence of reactive airways (wheeze, hyperinflation, tachypnoea)
- Assessment of lymphoid tissue, such as presence of tonsils and lymph nodes
- Skin signs, such as severe eczema, signs of persistent or frequent bacterial, viral or fungal skin infection
- Hepatosplenomegaly

Reference

Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS phenotypic classification of primary immunodeficiencies. J Clin Immunol 2018; 38: 129-143.

COMPETING INTERESTS: None