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Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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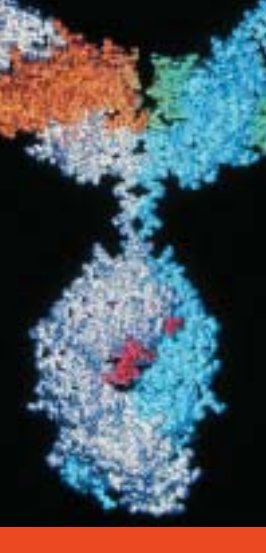
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IMMUNODEFICIENCY

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Immunodeficiency: clinical features and investigation

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Introduction

Immunodeficiency should be suspected whenever there is unusual, persistent or recurrent infection (about 10 or more infections a year). Immunodeficiencies are classified by cause (eg, primary versus secondary immunodeficiency, genetic basis, etc) and by phenotype (see table 1, next page, and table 2, page 4).

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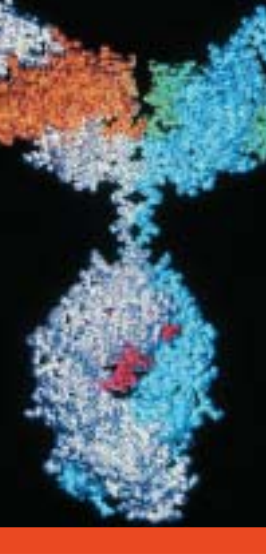
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Table 1: Primary immunodeficiency features and occurrence

Disorder	Cell type primarily affected	Mode of inheritance	Predominant features	Prevalence (approximate)
Selective IgA deficiency	B cells	Complex, polygenic. Associated with HLA haplotype A1, B8, DR3	Recurrent sinopulmonary and gastrointestinal infections, atopy, autoimmunity	1:1000
Common variable immunodeficiency	B cells, T cell function may be compromised	Complex, sometimes autosomal recessive	Bacterial infection, especially sinopulmonary, autoimmunity, lymphoma, other infections	1:20,000
Bruton's agammaglobulinaemia	B cells	X-linked	Absent or severely depleted immunoglobulins (all classes), bacterial infections from about six months, ECHO virus infections, arthritis	1:100,000
IgG subclass deficiency	B cells	Unknown	Bacterial infection, especially respiratory. May be associated with IgA deficiency	Unknown. Probably relatively common
DiGeorge anomaly	T cells, B cell function also affected	Hemizygous at 22q11	Immunodeficiency, unusual facies, thymic hypoplasia, hypocalcaemia, coronary heart disease	1:4000
Chronic mucocutaneous candidiasis	Selective defect in T cell function	Autosomal recessive	Chronic candidal infections, endocrinopathy. Early death if untreated	1:80,000
Severe combined immunodeficiency	T and NK cells depleted. B cells may be increased in number, but dysfunctional	Usually X-linked IL2 receptor gamma chain. Rarer autosomal recessive form	Failure to thrive and persistent, recurrent or severe fungal, viral and bacterial infections. Early death if untreated	1:50,000 — 1:100,000
Wiskott-Aldrich syndrome	T and B cells	X-linked	Thrombocytopenia, eczema, recurrent infection. Death in first decade in severe untreated cases	1:250,000
Chronic granulomatous disease	Neutrophils	X-linked or autosomal recessive	Deep-seated infection caused by staphylococcus, serratia marcescens, candida or aspergillus. Diffuse granulomata in respiratory, gastrointestinal or urogenital tracts. Failure to thrive and hepatosplenomegaly or lymphadenopathy	1:200,000
Hyper-IgE/Job's syndrome	Neutrophil chemotaxis defect	Sometimes autosomal dominant	Extremely high IgE, eczema, recurrent infection, especially <i>Staphylococcus aureus</i>	
Complement deficiencies		Most are autosomal recessive	Pyogenic infections, neisserial infections, autoimmunity	Vary, up to 1:20 000



Immune function tests

The assessment of immune competence is predicated upon which component/s of the immune system are affected. More severe immune deficiencies may involve multiple aspects of immune function.

Cellular:

- Cell populations (eg, lymphocyte immunophenotyping).
- Cellular function (eg, delayed type hypersensitivity responses).

Humoral:

- Quantitative. Measurement of concentrations of immunoglobulin classes and subclasses in serum and other body fluids.
- Qualitative. Assessment of immunoglobulins (monoclonal immunoglobulins or paraproteins).
- Functional. Concentrations of antigen-specific immunoglobulin pre- and post-vaccination.

Other:

- Neutrophil function tests — generally performed by specialist laboratories.
- Complement concentrations in serum.
- Cytokine concentrations and surrogate markers (eg, C-reactive protein as a surrogate marker for IL-6).

Most of these tests require expertise in performance and interpretation.

Table 2: Secondary immunodeficiency

Infections, including HIV
Malignancy
Drugs and radiation
Nutritional and metabolic disorders
Protein losing states
Splenectomy
Chronic renal disease
Stress and severe illness, trauma
Extremes of age

Case one

A mother brings in her five-month-old son because he screamed all night and she has been worried about his weight. He was a term delivery after an uncomplicated pregnancy, and at birth he was on the 50th centile for length, weight and head circumference. He has not fed well and his mother is worried that he seems not to attach to the breast.

He has had several episodes of diarrhoea. The clinic nurse advised the mother to seek medical attention because he is now falling below the 10th centile and the nurse had noted oral thrush at every visit. His vaccination schedule has been delayed by recurrent infections.

On examination, he is a small child who looks undernourished. He is febrile. He has severe oral thrush and the tonsils cannot be seen. He has right otitis media and a florid nappy rash. The GP prescribes an antibiotic and nystatin drops.

On review three days later he has not improved and now has a cough. Examination of the chest reveals bibasal crackles. A chest X-ray shows patchy alveolar shadowing and is remarkable for an absent thymic shadow. The radiologist is concerned about his immune competence.

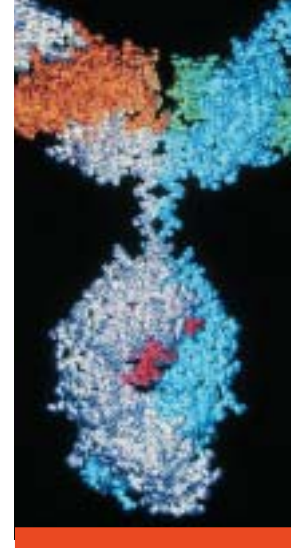
What tests should be done at this stage?

1. Full blood count. The notable feature is marked lymphopenia $0.2 \times 10^9/L$ ($2.2-7.0 \times 10^9/L$). The neutrophil and platelet counts are slightly low.
2. Immunoglobulins. IgG is at the lower limit of the age-adjusted reference interval, but IgM and IgA are undetectable.
3. HIV test — negative.

What is the significance of these results?

The lymphopenia is typical of primary cellular immunodeficiency.

Immunoglobulin levels are lowest in infancy because of physiological delay in immunoglobulin synthesis. Although some IgG of maternal origin may be present, it is being catabolised and replaced with the



infant's own IgG. Typically, this situation resolves in about two months, but if prolonged, is manifested as transient hypogammaglobulinaemia of infancy. Babies with humoral immunodeficiency syndromes have variable perturbation of all antibody classes, depending on the condition present.

In this child there is likely to be deficient synthesis of all immunoglobulin classes, but the defective IgG production is being temporarily masked by maternal antibody.

What is the most likely diagnosis?

This child shows defects in cellular immunity (persistent oral candidiasis, viral diarrhoea, probable pneumocystis carinii pneumonia, lymphopenia and an absent thymic shadow) and humoral immunity (severe bacterial infection and hypogammaglobulinaemia). The clinical picture and laboratory findings are typical of severe combined immunodeficiency (SCID).

What is the further management?

This child should be referred to a paediatric clinical immunologist for further investigation and treatment. Further investigation would begin with lymphocyte immunophenotyping.

Patients with SCID usually have severe CD4 lymphopenia, but because there are several genetic subtypes of SCID, assessment of B and NK cells are useful in classifying this condition. Tests of lymphocyte function and molecular genetics can more precisely identify the immunological defect.

Immediate management is aggressive treatment of the infections followed by secondary prophylaxis for candida and pneumocystis infections, and immunoglobulin replacement to avoid bacterial infection.

The definitive treatment for this child will be stem cell transplantation with an HLA identical donor, preferably a sibling. Alternatives include transplantation with a matched unrelated donor or with banked cord blood. Gene replacement therapy is still in development.

How does this diagnosis affect future management?

- Children with immunodeficiencies are potentially at risk from immunisation. This is particularly so for the live attenuated vaccines (see table 3, right). Once lymphocyte populations have reconstituted after transplantation, a vaccination schedule can proceed.
- All infections must be treated promptly and appropriately. Specimens for microbiological identification of the causative organism must be obtained before antibiotic therapy is started. Antivirals may also be required, so swabs in viral transport medium should also be collected.
- Any blood product that potentially contains white cells must be irradiated before transfusion.

Table 3: Live vaccines that should be avoided*

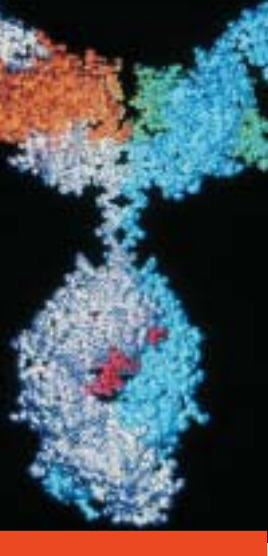
AGE	VACCINE
2 months	OPV
4 months	OPV
6 months	OPV
12 months	MMR
18 months	VZV
4 years	OPV, MMR
10–13 years	VZV

* Refer to the Australian Immunisation Handbook at www1.health.gov.au/handbook

Case two

A 17-year-old girl presents in mid-January with severe earache. She has had a “cold” for five days, and describes a life-long pattern of “colds” that go to her chest or and require antibiotic treatment. She says she catches everything that goes around, especially respiratory and gastrointestinal infections. She gets hayfever in spring and summer, and is allergic to house dust mite and penicillins. She has had a tonsillectomy.

On examination, she has right otitis media. The left tympanum does not have a good light reflex. There is some facial tenderness over the frontal sinuses. The chest is clear.



What tests should be done?

1. Full blood count. The only abnormality is a neutrophilia associated with the bacterial infection.
2. Immunoglobulins. IgM 1.6g/L (0.5-3.0g/L), IgG 8.2g/L (6.5-16g/L), IgA <0.1g/L (0.6-4.0g/L).

What is the significance of these results?

There is isolated deficiency of IgA. This concentration of serum IgA is typical of selective IgA deficiency. Because there is often associated IgG subclass deficiency, especially in symptomatic patients (33-50%), the levels of IgG subclasses should be measured. Deficiencies of immunoglobulins are associated with persistent or recurrent bacterial infections.

What is the most likely diagnosis?

Selective IgA deficiency. IgA is present in two subclasses (IgA1 and IgA2) and is present on B lymphocytes, in serum and on mucosal surfaces. Symptoms are reportedly more severe in patients with deficiency of IgA2, but in practice, only total IgA is requested.

What is the further management?

Antibiotic therapy is indicated because the infection is likely to be persistent.

While treatment of other immunoglobulin deficiencies may involve immunoglobulin replacement, replacement immunoglobulin is **not** indicated for isolated IgA deficiency and may sensitise the patient to the low levels of IgA present in immunoglobulin preparations, which have variable amounts of IgA. Development of anti-IgA antibodies may lead to anaphylaxis during blood transfusion unless special precautions are taken. For this reason, all patients should wear a Medic Alert bracelet or similar.

Other issues

Patients with IgA deficiency are prone to several manifestations of immune dysregulation. The most common problem is allergy, especially allergic sinusitis and food intolerances. Most autoimmune diseases are more prevalent in those with IgA deficiency, including SLE, rheumatoid arthritis, dermatomyositis, hypothyroidism, coeliac disease, pernicious anaemia, chronic active hepatitis, autoimmune haemolytic anaemia and dermatitis herpetiformis. Certain malignancies are also increased.

Selective IgA deficiency clusters in families, but no single gene defect can be found in all cases.

Case three

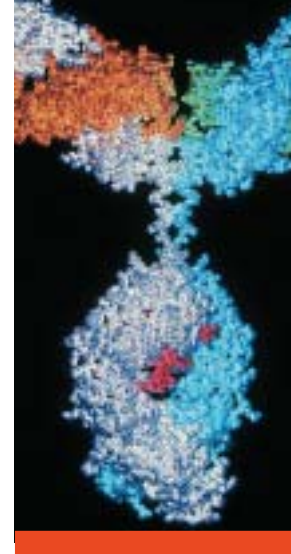
A married 40-year-old man presents with a four-week history of diarrhoea and weight loss of 10kg. He has had intermittent fevers and nocturnal sweats for the previous three weeks. He returned from his most recent trip to South-East Asia about five weeks ago.

On examination he is thin and has palpable cervical and bilateral axillary lymph nodes. He has a fever (38.2°C). There are whitish plaques on the tongue and pharynx. Cardiovascular and respiratory examinations are unremarkable. His abdomen is soft and mildly tender, with no palpable masses.

What is the differential diagnosis for these clinical findings?

He has multiple symptoms, each of which could be associated with infection or malignancy. There are many infectious causes of diarrhoea and the clinician should look for pathogens found in South-East Asia, including campylobacter, giardia, amoebiasis, microsporidium, cryptosporidium, mycobacteria and cytomegalovirus. Other conditions that should be considered include inflammatory bowel disease, coeliac disease, and other causes of malabsorption.

The whitish plaques in the oropharynx are most likely caused by candida infection, which should alert the doctor to the possibility of immunodeficiency.



What investigations are indicated?

The wide differential diagnosis means the following initial investigations are indicated:

1. Full blood count. There is a neutrophilia $10.5 \times 10^9/L$ ($2.0-7.5 \times 10^9/L$), mild lymphopenia $0.8 \times 10^9/L$ ($1.5-4.0 \times 10^9/L$) and mild thrombocytopenia $100 \times 10^9/L$ ($150-400 \times 10^9/L$).
2. Urea and electrolytes. Sodium 140mmol/L ($135-145 \text{mmol/L}$), potassium 3.0mmol/L ($3.5-4.5 \text{mmol/L}$), creatinine 0.13mmol/L ($60-120 \text{mmol/L}$).
3. Liver function test. The AST is 45 U/L ($<40 \text{ U/L}$) and the ALT is 50 U/L ($<35 \text{ U/L}$).
4. Stool microscopy and culture. Microscopy is negative for red and white blood cells, cysts, ova and parasites. Culture is negative.
5. BSL — normal.

What other investigations are indicated?

The lymphopenia and deranged LFTs suggest viral infection. Serology for hepatitis viruses, cytomegalovirus, Epstein-Barr virus and HIV are indicated. Pre-test counselling and patient consent are essential before requesting HIV serology. The hepatitis A, B and C serology and hepatitis BsAg are negative. Epstein-Barr and cytomegalovirus are both positive for IgG antibodies, but negative for IgM antibodies, indicating previous infection.

Depending on the clinical history provided, the laboratory may report the result of a combined antigen/antibody test for HIV, rather than a simple IgG antibody result. This is clearly important in this case in which acute HIV seroconversion illness is a possibility. The combined HIV Ag/Ab test is positive.

Although these tests have a specificity of more than 99.85%, they may give non-specific reactions because of other causes, such as other viral infections. Therefore, this result must be confirmed on a new specimen.

The second specimen can be also used for supplementary HIV-specific testing. If testing is done early in seroconversion, the results may be inconclusive and serial repeat testing is mandatory.

What is the further management?

1. This patient needs to be referred to a doctor with experience in HIV medicine. He will undergo serial tests of immune function (CD4+ T lymphocyte count) and assessment of HIV viral load. Results six months after seroconversion have been shown to be independent predictors of disease progression.¹
2. The relevant authorities should be notified. HIV is a notifiable disease in all Australian states.
3. The patient's wife should be tested for HIV and sexual contacts should be traced following usual procedures in your state.
4. Education about safe sex practices is mandatory.

Key points

- Immunodeficiency is extremely variable in presentation and severity reflecting the different components of the immune system that may be affected, singularly or in combination.
- Doctors should maintain a high index of suspicion because delay in diagnosis may contribute to morbidity and mortality.
- HIV infection may occur at any age and another disease may be a presenting feature (eg, malignancy).
- Immunodeficiency may be associated with and complicated by other disease processes (eg, autoimmune disease).
- Immunodeficiency may affect families by inheritance, transmissibility or its psychosocial effects.
- All patients with suspected immunodeficiency should see an immunologist at least once, and those with primary immunodeficiency should be entered on the Primary Immunodeficiency Registry.
- Assessment of family members may be required.

1. Mellors JW et al. *Annals of Internal Medicine*. 1997; 126:946-54.