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Does this patient have an immunodeficiency?

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There is a good chance that most physicians will have seen a patient with an immune deficiency in the past year. This brief review aims to help decide when a patient needs to be investigated for immunodeficiency, what tests should be done and what to do with the results. Detailed descriptions of individual immunodeficiency disorders can be found in reviews listed.[1–3] Children with suspected immunodeficiency require special consideration and are outside the scope of this article.

Epidemiology and missed diagnoses

HIV infection is the most common cause of secondary immunodeficiency for which prevalence data are available. It is estimated that 0.2% of men and 0.1% of women in the UK are infected, approximately one-quarter of them undiagnosed.[4] Neutropenia and other secondary and iatrogenic immunodeficiencies are common but their prevalence is difficult to quantify. The prevalence of common variable immunodeficiency (CVID), the most common primary antibody deficiency, is at least one in 50,000 in the UK but it is likely that many cases are unknown. International estimates of prevalence of CVID are as high as one in 10,000. Selective immunoglobulin A deficiency is common (1 in 500–700) but most of these individuals are asymptomatic and do not suffer from infections. Complement, primary T lymphocyte and neutrophil disorders are relatively rare.

There is also a significant delay in the diagnosis of immunodeficiency: 52% of adults with HIV infection are diagnosed late and 30% very late. In primary antibody deficiencies, delays of over seven years between first presentation and final diagnosis are common. For both diseases patients have often been reviewed by several physicians without the diagnosis having been considered. Delays in diagnosis and treatment are associated with poor outcomes.

Key points

Patients with immunodeficiency often present with infections but these need not be unusual or severe

Immunodeficiency presenting in adults may be secondary (eg HIV, lymphoma, drugs) or primary (usually antibody deficiency)

FISHing (full blood count, immunoglobulins, serum complement, HIV test) will identify the most common immunodeficiencies

Adults with normal initial investigations may nonetheless have significant immunodeficiency: referral to an immunologist is recommended where there is a high index of suspicion

Non-infectious features such as splenomegaly, granulomata or autoimmunity (eg idiopathic thrombocytopenic purpura) increase the likelihood of identifying an immunodeficiency

KEY WORDS: common variable immunodeficiency, HIV infection, immunoglobulins, primary immunodeficiency, secondary immunodeficiency

When should immunodeficiency be considered?

Immunodeficiency should always be considered in patients with severe, persistent, unusual or recurrent infections. HIV testing should be specifically offered in a range of common conditions, including tuberculosis, atypical pneumonia, lymphoma, hepatitis B and C infection, as well as with well-known AIDS-defining illnesses (Kaposi's sarcoma, pneumocystis, cryptococcal or toxoplasma infections and oesophageal candida). In such circumstances, if HIV tests are negative, wider screening for immunodeficiency is often warranted. Infections and other presentations that should cause concern are included in Table 1.

Iatrogenic secondary immunodeficiency is often suspected from the clinical circumstances (eg recent chemotherapy or immunosuppression). Less well-known causes of secondary immunodeficiencies include hypogammaglobulinaemia with some anticonvulsants and antirheumatic drugs (eg sulphazalazine, gold). With some newer biological agents (eg antitumour necrosis factor drugs, rituximab), the infection risk may not be fully recognised for many years after they are licensed.

Contrary to common perception, primary immunodeficiency often presents for the first time in adulthood. Recent UK guidelines for bronchiectasis specifically recommend testing for immunodeficiency in all cases. Other conditions such as sarcoid (or other granulomatous conditions), inflammatory bowel disease, lymphoma, immune thrombocytopenic purpura and neutropenia should also trigger immunodeficiency investigations.

Sometimes it is not the infection itself but the associated features which should prompt consideration of immunodeficiency. Paradoxically, autoimmunity is increased in immunodeficiency. Infections occurring in patients with splenomegaly, cytopenias (neutrophils, lymphocytes or platelets), chronic diarrhoea, sarcoid or coeliac disease should be investigated further (Fig 1).

While recurrent meningitis is the hallmark of complement deficiency, not all complement disorders present with infections. Patients with a strong family history or early presentation of lupus or immune complex diseases should be investigated for complement defects with a CH50 functional complement test. Infections are not a feature of C1 inhibitor deficiency (inherited or acquired); these patients present with recurrent angio-oedema.

Laboratory investigations

Laboratory evidence of immunodeficiency may be identified indirectly during the course of routine testing for vague clinical presentations. Neutropenia, and especially lymphopenia, are often ignored or attributed to other causes and not further investigated. Low serum globulins (total protein minus albumin should be >20 g/l) may be seen in hypogammaglobulinaemia. Similarly raised globulins

Case 1

A 30-year-old man presented to his GP with anorexia and generalised aches and pains for six months. Investigations showed normal full blood count, renal and liver function. A grossly elevated serum total protein (95 g/l) was noted. Raised erythrocyte sedimentation rate (35 mm/hr) and weakly positive antinuclear antibodies were also identified. In view of the raised globulins, serum immunoglobulin (Ig) levels were tested and showed polyisotypic hypergammaglobulinaemia (IgG 45 g/l (6–16), IgA 10 g/l (0.8–2.8) and IgM 6 g/l (0.5–1.9)), with a polyclonal pattern on electrophoresis. After a brief pretest discussion with the patient, tests confirmed HIV infection and a marked CD4 lymphopenia (150 cells/mm^3) – a very late diagnosis.

Case 2

A 60-year-old woman presented after two episodes of bronchopneumonia which had responded to broad-spectrum antibiotics. Clinical examination showed enlarged cervical lymph nodes and palpable spleen. An HIV test was negative. Serum immunoglobulins (Igs) showed reduced IgG with normal IgA and IgM and no paraprotein. She showed a good antibody response to tetanus vaccination but no response to the unconjugated pneumococcal vaccine. Lymph node biopsy identified follicular lymphoma. Her secondary hypogammaglobulinaemia was managed with prophylactic antibiotics, but Ig replacement therapy was also considered.

Table 1. Reasons to go FISHing.[5]

Specialty	Presentation
Respiratory	Bronchiectasis, recurrent upper or lower respiratory infections, sweat test requested, granulomatous disease, sarcoid, TB, bilateral infiltrates, atypical pneumonia, pneumocystis, non-response to pneumococcal vaccine
ENT	Recurrent otitis media, glue ear, grommet insertion, recurrent or persistent candida, granulomatous parotitis
Gastroenterology	Diarrhoea, weight loss, IBD, coeliac disease, non-coeliac sprue, recurrent salmonella, giardia or cryptosporidium, hepatitis B or C, non-response to Hep B vaccine, oral or oesophageal candida, oral hairy leucoplakia
Haematology	Raised ESR, lymphadenopathy, splenomegaly, anaemia, thrombocytopenia, neutropenia, lymphopenia, lymphocytosis, lymphoma, absent isohaemagglutinins
Rheumatology	Arthritis, early-onset or familial connective tissue disease, ANCA-associated disease, infection after disease-modifying therapy
Neurology	Meningitis, encephalitis, toxoplasmosis, cerebral lymphoma, cryptococcal meningitis
Dermatology	Recurrent abscesses, Kaposi's sarcoma, recurrent or persistent warts, recurrent or extensive shingles, alopecia
Oncology	Lymphoma, radiation sensitivity
Ophthalmology	

ANCA = antineutrophil cytoplasmic antibody; CMV = cytomegalovirus; ENT = ear, nose and throat; ESR = erythrocyte sedimentation rate; FISH = full blood count, immunoglobulins, serum complement C3/C4, HIV test; IBD = inflammatory bowel disease; TB = tuberculosis.

(>40 g/l) can occur in HIV infection and myeloma and should prompt further tests. Failure to produce an antibody response to vaccination or infection, or absent isohaemagglutinins (blood group antibodies) may also be pointers to antibody deficiency.

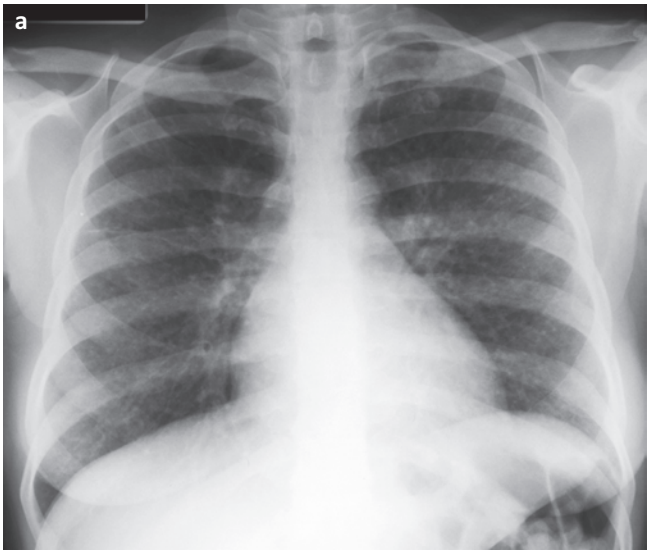
Testing for immunodeficiency: go 'FISHing'

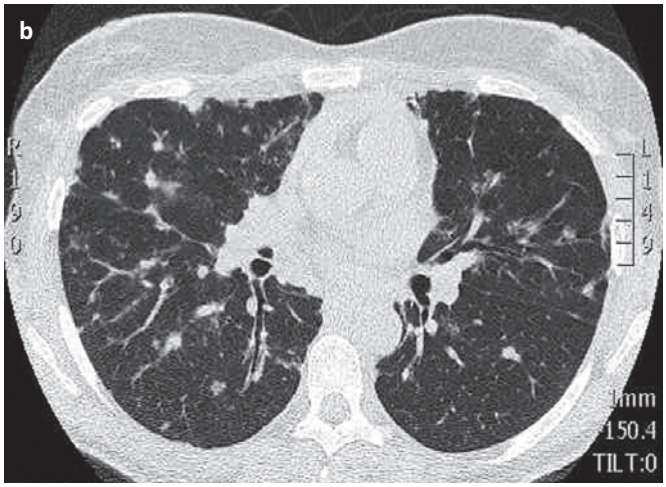
The tests indicated depend on the most likely diagnosis. This is suggested by a combination of the presenting features and prevalence of the condition. For example, meningococcal meningitis is a classic presentation of a complement deficiency, but antibody deficiencies are more likely to be identified because they are commoner. Fortunately, the most common immunodeficiencies can be identified on simple and widely available tests. In a busy clinical environment, the acronym FISH (full blood count, immunogloblins, serum complement C3/C4, HIV test) is a mnemonic for the common first-line investigations. These initial tests are occasionally diagnostic but usually only provide pointers to the problem (Table 2a). Scrutiny of the results with follow-up of any abnormality is essential (Table 2b).

Further investigations

A comprehensive algorithm for investigation of immunodeficiency has been published[5] and is also available as a web-based tool (www.ukpin.org.uk). Discussion with an immunologist is recommended for cases where abnormalities of uncertain significance are found or immunodeficiency is strongly suspected despite normal investigations.[6] Immunodeficiency disorders not identified on routinely available tests include specific antibody deficiency, complement deficiency, chronic granulomatous disease or type 1 cytokine deficiency. These can be identified only by requesting the specific diagnostic test on the basis of a high index of suspicion and knowledge of the typical presentations of the individual diseases.

When the investigation of immunodeficiency is being considered, discussion of appropriate microbiological investigations should take place at the same time. Specialised culture or molecular tests for a wider range of organisms may be indicated. It is worth noting that viral and bacterial serology will be unreliable in patients with antibody deficiency. Similarly, interferon-gamma release





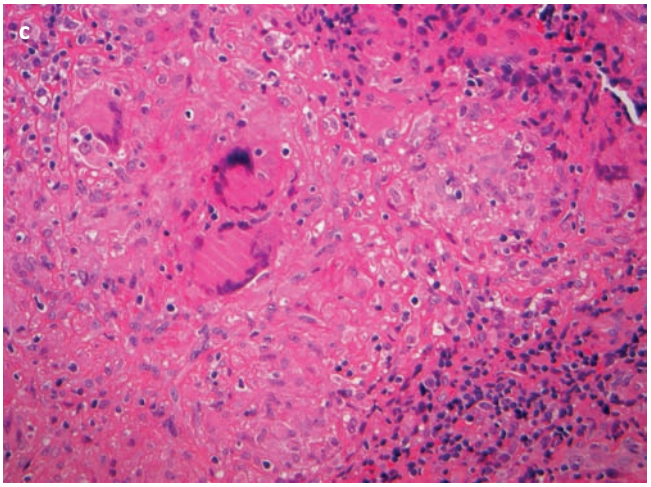


Fig 1. (a) Chest X-ray of a 26-year-old woman presenting with a dry cough showing bilateral hilar lymph node enlargement and perihilar parenchymal nodularity. (b) Computed tomography image better demonstrates the parenchymal nodules with a perilymphatic distribution consistent with granulomatous inflammation. Lung function tests show a restrictive pattern and reduced carbon monoxide transfer factor. **(c) Transbronchial biopsy shows non-caseating granulomas, including some giant multinucleated cells of the Langerhans type.** After exclusion of tuberculosis and HIV, sarcoidosis was diagnosed and she was treated with steroids. Four years later, after two episodes of lobar pneumonia, serum immunoglobulins (Igs) were measured and found to be reduced. A diagnosis of common variable immunodeficiency was made and she was commenced on Ig replacement therapy. It was revealed that she was non-immune to rubella during her pregnancies at ages 20 and 22, suggesting that a significant immunodeficiency had been present for at least 10 years (images courtesy of Drs John Reynolds and Zbigniew Rudzki).

assays (eg to investigate tuberculosis) may also be falsely negative in immunosuppressed patients.

Finally, some patients clearly have abnormal susceptibility to infection but do not fall into any currently known disease pattern. These patients should be referred for immunology specialist follow-up. It is in this environment that rare and new diseases will continue to be investigated, and where the interface of the basic science and clinical practice of immunology helps to advance understanding and therapy of the immune system.

Conclusions

The question 'Does this patient have an immune deficiency?' should be asked in a wide range of clinical scenarios in which infection need not be a prominent feature. The situation is analogous to cystic fibrosis, coeliac or thyroid disease which are increasingly diagnosed in patients who lack the classic features of the condition. Widely available, simple tests can often suggest the diagnosis, but further tests and specialist referral are indicated where there is a high index of suspicion. There remains a perception that HIV testing is awkward and patients (and many doctors) still avoid discussing it. Until the HIV test becomes an 'ordinary' investigation in routine practice, this condition will remain underdiagnosed to the detriment of the patient and the public. We recommend

Table 2a. Investigation of possible immunodeficiency (ID): FISHing for immunodeficiency. This will identify many primary and secondary IDs but other important conditions require further tests (see Table 2b).

	Finding	Significance with respect to ID	Possible next steps
Full blood count	Low neutrophils	Secondary or primary neutropenia; autoimmune associated with immunodeficiency; rarely T cell neoplasia.	Haematology/immunology opinion
	High neutrophils	Reactive.	Immunology opinion
	Low platelets (or low platelet volume)	Autoimmune disease (eg in immunodeficiency); Wiscott-Aldrich syndrome	See Table 2b, B3
	Low lymphocytes	HIV; steroids; cytotoxic drugs; primary T/B cell deficiency	Lymphocyte subsets*
	High lymphocytes	Viral infection; leukaemia; lymphoma	Lymphocyte subsets* As suggested by other parameters
	Anaemia	Anaemia of chronic disease, malabsorption, autoimmune haemolysis may all occur in immunodeficiency	Lymphocyte subsets*; immunology opinion
	High eosinophils	Rarely lymphoma; some infections; hyper-IgE syndrome	
Immunoglobulins	High IgG, A, M	Chronic infections (with or without immunodeficiency); HIV; neutrophil defects; T cell lymphoma	See Table 2b, B1,3 or 5
	Low IgG	Protein loss;drugs; lymphoid neoplasia; primary immunodeficiency; thymoma	See Table 2b, B1
	Low IgA	Often asymptomatic	If infections, see Table 2b, B1
	Low IgM	Drugs; uraemia; myeloma (light-chain, non-secretory); other lymphoid neoplasia	Haematology/immunology opinion
	Paraprotein	Reactive; myeloma; other lymphoid neoplasia	Haematology opinion serum/urine free light chains
Serum complement C3/C4	Low C3	Rarely congenital C3 or regulatory factor deficiency	Immunology opinion
	Low C4	Partial genetic deficiency; cryoglobulinaemia; C1 inhibitor deficiency (hereditary or acquired)	Immunology opinion See Table 2b, B6
HIV test	Positive	Probable HIV infection	Refer to HIV team Lymphocyte subsets*

FISH = full blood count, immunogloblins, serum complement C3/C4, HIV test; ID = immunodeficiency; Ig = immunoglobulin.

Table 2b. Investigation of possible immunodeficiency: results of FISHing normal, nothing significant, or follow-up testing. A guide to possible second- and third-line investigations (it is often helpful to consult an immunologist at this stage). Adapted from reference 6.

Presentation	Suggested next investigation	Possible further tests
B1 Recurrent upper or lower respiratory infection, infections with encapsulated organisms (eg haemophilus, pneumococcus)	Vaccine challenge;** IgG subclasses	Lymphocyte subsets*
B2 Meningitis, recurrent meningococcal or gonococcal infections	Complement function (CH50, AP50); vaccine challenge**	MRI base of skull
B3 Unusual/opportunistic infections	Lymphocyte subsets*; repeat HIV test; neutrophil function	Lymphocyte phenotyping and proliferation, cytokine studies
B4 Recurrent fevers	Consider cyclical neutropenia: neutrophil count ×3/week for six weeks Consider periodic fever syndromes: immunology or national referral centre	
B5 Pyogenic infection, septicaemia	Blood film (polymorph granules, Howell-Jolly bodies); neutrophil function; neutrophil count ×3/week for six weeks; complement function (CH50, AP50); splenic ultrasound	
B6 Angio-oedema (without urticaria)	C1 inhibitor levels and function, C3/C4 during an attack	

*Enumeration of individual lymphocyte subsets using antibodies to CD3, CD4, CD8, CD19, CD16/56 as a minimum panel.
**Vaccine challenge: test vaccine-specific antibodies before and 3–4 weeks after vaccination. Unconjugated pneumococcal polysaccharide (eg Pneumovax), tetanus and Haemophilus influenzae type B conjugate vaccines commonly used. Live and live-attenuated vaccines should never be given to patients suspected of having immunodeficiency.
FISH = full blood count, immunogloblins, serum complement C3/C4, HIV test; MRI = magnetic resonance imaging.

immunodeficiency testing in a wider range of disease-specific diagnostic protocols. FISHing is encouraged, but it is important to examine the results critically and to recognise the potential significance of results which might suggest an immunodeficiency only indirectly.

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Box 1. Useful sources of information about immunodeficiency.

www.UKPIN.org.uk	UK Primary Immunodeficiency Network Find an immunologist, online diagnostic algorithm
www.isitpid.com	Is it PID? Multidisciplinary campaign to increase primary immunodeficiency awareness among non-immunologists
www.PiA.org.uk	UK patient support group for primary immunodeficiencies
www.primaryimmune.org	Excellent primary immunodeficiency information for physicians and patients

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