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Primary antibody deficiencies: recognition, clinical diagnosis and referral of patients

Philip Wood on behalf of a working party of the UK Primary Immunodeficiency Network*

ABSTRACT – The primary antibody deficiency syndromes are a rare group of immunodeficiencies where diagnostic delay remains common due to limited awareness of the existence and heterogeneity of their presenting features. Referral for specialist assessment leads to earlier diagnosis and appropriate therapy to prevent or limit structural organ and tissue damage. Greater education of healthcare professionals is required to ensure prompt recognition and referral to specialists with expertise in the care of primary immunodeficiencies, especially since study of these rare conditions is a minor part of undergraduate and general postgraduate training. Greater awareness would lead to reduced morbidity, improved quality of life and survival outcomes in this patient group.

KEY WORDS: common variable immunodeficiency disorders, immunoglobulin therapy, primary antibody deficiency, X-linked agammaglobulinaemia

Purpose

The main objective of this guideline is to inform clinicians about the varied and frequently complex presentations of primary antibody deficiency syndromes and to emphasise the importance of early recognition, diagnosis and referral for appropriate treatment. Specifically, the guideline offers recommendations on the identification of those patients who should be referred to clinical immunology services that are supported by expert specialist immunology laboratory services.

The guideline applies to those patients with the whole spectrum of clinical problems related to primary antibody deficiencies, with the aim of ensuring equity of access to consistently good care and has been developed for the guidance of healthcare professionals who, in their clinical practice, may encounter patients with unsuspected primary antibody deficiencies.

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*This guidance was prepared on behalf of a working party of the UK Primary Immunodeficiency Network. For membership of the party, see the end of paper.

Implications for implementation

These guidelines are intended to impact primarily on education of healthcare professionals and their awareness of primary antibody deficiency. All clinical staff within the hospital setting should consider the possible diagnosis of primary antibody deficiency in a patient presenting with severe, persistent, opportunistic or recurrent infections or with other potential indicator conditions. The latter includes disorders of immune regulation (granulomatous, hypersensitivity or autoimmune disease), a restricted range of malignant diseases (lymphoma, skin or gastric cancer), vaccine failures or, occasionally, stigmata associated with specific deficiency syndromes.

Recognition and referral of patients with suspected primary antibody deficiency is important as appropriate therapy can prevent or reduce infections, and delayed therapy is associated with complications.

Primary antibody deficiency syndromes (Table 1)

Prevalence and clinical presentation

The prevalence of clinically significant primary antibody deficiency is around 1:25,000 to 1:110,000 of the population. Overall, 95% of patients with primary antibody deficiencies present after the age of six years. A relevant history allied to appropriate suspicion and disease awareness, are the most important elements for early recognition and diagnosis of primary antibody deficiency. Patients at any age with recurrent infections (especially in the upper and lower respiratory tracts), those with infections in more than one anatomical site and those in whom the frequency or severity of infection is unusual or out of context should be investigated for possible antibody deficiency (Table 2). More rarely, granulomatous, inflammatory or autoimmune features are the initial manifestation of primary antibody deficiency. The European Society for Immunodeficiencies (ESID) has developed an algorithm for clinicians to guide assessment and referral of possible primary immunodeficiencies, including primary antibody deficiencies.[1] The UK Primary Immunodeficiency Network website contains a diagnostic tool developed from this algorithm to help clinicians assess potential primary immunodeficiency disorders (www.ukpin.org.uk).

Investigations

Serum immunoglobulins are the most important investigation in initial assessment. Most patients subsequently diagnosed with

The guidelines

Key recommendations

	Recommendation	Grade	Level of evidence
1	Primary antibody deficiency should be considered in all patients with severe, persistent, unusual or recurrent infections	B	2++
2	Serum immunoglobulins should be measured in any patient with severe, persistent, unusual or recurrent infections	B	2++
3	Reduced levels of any of the three major immunoglobulin isotypes (IgG, IgA and IgM) in the serum should prompt referral to a clinical immunologist	D	4
4	Normal levels of immunoglobulin do not exclude a diagnosis of primary antibody deficiency and referral to a clinical immunologist for further investigations should be considered in any individual with severe, persistent, unusual or recurrent infections	C	2
5	Individuals with suspected or proven primary antibody deficiency should be referred to a clinical immunologist	D	4
6	All patients with a proven primary antibody deficiency should receive immunoglobulin replacement therapy as it increases life expectancy and leads to a reduction in the rate of bacterial infection – higher doses may provide additional benefit	A	1+
7	All patients with a primary antibody deficiency should be monitored regularly for the occurrence of acute infection, even when receiving immunoglobulin replacement therapy	B	2++
8	All patients with a primary antibody deficiency should be monitored regularly for the development of disease complications	B	2++
9	The management of all patients with any form of primary antibody deficiency should be led by a clinical immunologist with appropriate training and experience	D	4
10	Patients should be offered a choice of route (intravenous or subcutaneous) and location (hospital or home) for immunoglobulin replacement therapy if appropriate	B	2++

Good practice points

- A clinical immunologist should initiate treatment with immunoglobulin, after full risk assessment for that patient and provision of written information
- Patients should start therapy in an established immunology centre where specialist immunology nurses can assist with their management
- Specialist immunology nurses should be involved in ongoing management of patients receiving therapy both in the home or hospital setting
- All patients should have the opportunity to be assessed for home therapy if appropriate. Such 'home therapy' programmes are available in specified centres. Guidelines for home immunoglobulin therapy have been approved by the professional medical bodies and by the Department of Health
- Clinical immunologists should continue to review patients regularly on an outpatient basis in order to detect and treat disease progression or onset of complications, assess possible prognostic factors and carry out regular risk assessments for continuing treatment with immunoglobulin or other therapeutic agents
- In patients with structural lung damage, joint management with a respiratory physician should be considered, with the use of prophylactic antibiotics and physiotherapy as required on an individual basis
- Shared care between the clinical immunologist, local organ-based consultant and general practitioner will always be necessary to ensure adequate patient support, prompt treatment of breakthrough infections with appropriate antibiotics and optimal monitoring of remotely delivered immunoglobulin therapy
- Centres delivering care to patients with primary antibody deficiencies should be part of the national governance framework established by the United Kingdom Primary Immunodeficiency Network – a multi-professional grouping of healthcare professionals involved in the delivery of care to patients with primary antibody deficiencies (www.ukpin.org.uk)

Table 1. B-cell defects. (a) Early B-cell differentiation defects; (b) later B-cell differentiation/function defects.

(a)

Disease	B cells	Immunoglobulins (Ig)	Inheritance	Gene defect	Mechanism
XLA	Absent/low	All reduced	X-linked	Btk	B-cell differentiation failure
Abnormalities in pre-B cell receptor complex	Absent/low	All reduced	Autosomal recessive	Ig μ (mu) heavy chain CD79 α, CD79 β, λ5 surrogate light chain BLNK	B-cell differentiation failure

(b)

Disease	B cells	Immunoglobulins (Ig)	Inheritance	Gene defect	Mechanism
CVID-like syndromes	≥1%	LOW IgG and IgA with normal/raised IgM	Not consistently defined	Homozygous defects eg ICOS, TACI Heterozygosity/polymorphism eg TACI, Msh5	B-cell function failure
Ig-CSR deficiencies	Normal	Normal/raised IgM LOW IgG and IgA	AR	CD40	T-cell cooperation failure
			AR	AID	
			AR	UNG	
			X-linked	CD40 ligand	

AID = activation-induced cytidine deaminase; BLNK = B cell linker; CVID = common variable immunodeficiency disorders; ICOS = inducible co-Stimulatory receptor; IG-CSR = immunoglobulin class switch recombination; TACI = transmembrane activator and calcium-modulator and cyclophilin-ligand interactor; UNG = uracil-N-glycosylase; XLA = X-linked agammaglobulinaemia.

Table 2. Presenting symptoms of infection in cohorts of patients with primary antibody deficiencies.

Site of infection	Range reported (%)
Respiratory/chest infections including pneumonia (excluding 'bronchitis')	37–90
Recurrent sinus infections	19–98
GI infections	6–38
Cutaneous infections	1–13
CNS/meningitis	2–9
Septic arthritis/osteomyelitis	1–7
Ophthalmic	1.4–10

CNS = central nervous system; GI = gastrointestinal.

Table 3. Common acute infections in primary antibody deficiency.

Infection	Common causative organisms
Sinopulmonary	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphlyococcus aureus*
Septic arthritis	*Streptococcus pneumoniae Mycoplasma spp*
Genito-urinary	*Ureaplasma spp*
Meningitis	*Streptococcus pneumoniae, Haemophilus influenzae*
Gastrointestinal	*Cryptosporidium spp, Giardia spp Campylobacter spp*
Meningoencephalitis	Enteroviruses

primary antibody deficiency have an immunoglobulin (Ig) G level of 3 g/l or less, with an IgA level of less than 0.1 g/l and in some antibody deficiencies an IgM level of less than 0.25 g/l.[2,3] Over 90% of patients with the most common types of antibody deficiency, common variable immunodeficiency disorders, have an IgG level of less than 4.5 g/l at diagnosis.[4]

Diagnostic delay

Patients with primary antibody deficiencies present to a wide variety of clinical specialties other than clinical immunology, but the diagnosis of antibody deficiency is established in far fewer patients seen in these departments than in patients seen in immunology clinics. Diagnostic delay is associated with considerable morbidity, particularly recurrent pneumonias, with secondary structural lung damage such as bronchiectasis and associated pulmonary hypertension and, ultimately, pulmonary heart disease.[5]

Therapy

Immunoglobulin therapy increases survival, leads to a reduction in the rate of bacterial infections, days of antibiotic usage, days of fever and hospital admissions and is equally efficacious in this respect when given by either intravenous (iv) or subcutaneous (SC) routes.[2,4,6–8] Inadequate immunoglobulin replacement therapy or delayed diagnosis places the patient at greater risk of local or systemic recurrent infections. Some of the more common infections are listed in Table 3. The risk of infection

Table 4. Summary of organ-specific complications.

Respiratory
Respiratory symptoms are the most common presenting feature of primary antibody deficiencies
Granulomatous disease can occur in the respiratory tract
Bronchiectasis and bronchial wall thickening occurs in 17–76% patients
Gastrointestinal
Chronic diarrhoea occurs in 40–60% patients
Infectious diarrhoea occurs in 5–32% patients
Villous atrophy is present in 2.5% patients
Granulomata can occur anywhere in the gastrointestinal tract
Nodular lymphoid hyperplasia found in 0.5–30% patients
Others:
Atrophic gastritis
Pernicious anaemia
Inflammatory bowel disease, particularly with granulomatous appearances
Hepatic
Infectious hepatitis is rare
Abnormal liver function tests are commonly due to nodular regenerative hyperplasia in common variable immunodeficiency disorders
Hepatomegaly occurs commonly, often with granulomatous histology
Primary biliary cirrhosis
Sclerosing cholangitis is an unusual complication (particularly if infection with cryptosporidia)
Haematological
Immune thrombocytopenic purpura, autoimmune haemolytic anaemia, Evans syndrome and neutropenia occur in 2.5–11% patients
Overall haematological complications occur in 30% patients
Malignancy
Risk is increased 1.8–13-fold
Lymphomas are the most common
Epithelial malignancy occurs more rarely
Neurological
Encapsulated bacterial infections are the most common cause of meningitis
Enteroviral meningoencephalitis
Unexplained neurodegenerative disease can occur despite intravenous immunoglobulin therapy – though some of the signs may mimic vitamin E deficiency
Rheumatological
Non-specific arthritides
Bone and joint infections
Association with immune-mediated connective tissue diseases is rare
Cutaneous
Infection
Granulomata

remains even when appropriate therapy with replacement immunoglobulin is initiated, although this is reduced compared to untreated patients.

Complications

Despite therapy, patients can develop a number of organ-specific and systemic complications (Table 4), not all of which are related to diagnostic delay or inadequate replacement therapy with immunoglobulin. Some of these occur rarely and require specialist knowledge and experience for appropriate diagnosis and management.

Health-related quality of life (QoL) in untreated or inadequately treated primary antibody deficiency is poor in many areas of daily life. Optimal treatment with subcutaneous immunoglobulin dramatically improves QoL to levels comparable with normal control groups.[9]

Individual needs

In addition to medical needs, patients often require support with issues surrounding employment, travel and other insurance, access to appropriate benefits and support for carers and families. The Primary Immunodeficiency Association provides a vital function in these areas within the UK, and all patients should be provided with information about this organisation.

Membership of the working party

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