EDUCATION & DEBATE

Fortnightly Review

Consensus on diagnosis and management of primary antibody deficiencies

H M Chapel for the Consensus Panel for the Diagnosis and Management of Primary Antibody Deficiencies

Primary antibody deficiency syndromes include congenital and acquired antibody deficiencies but not those secondary to other diseases such as myeloma, chronic lymphocytic leukaemia, or protein losing enteropathy. Hypogammaglobulinaemia was the diagnosis usually given to patients with low serum immunoglobulin concentrations without an identifiable cause, but these patients are more accurately described as having primary antibody deficiency. There is a range of primary antibody defects (box),[1] though the clinical significance of some subgroups has been recognised only recently.[2-4]

The diagnosis of a primary antibody deficiency is often overlooked in both children and adults. Untreated patients with unrecognised primary antibody deficiencies suffer from recurrent infections, some of which may be severe—for example, pneumonia and meningitis.[2 5] In addition, they may have long term complications, such as enteropathy leading to malabsorption and anaemia.[6] About half of the patients without a diagnosis will be admitted to hospital every year; they may also be seen in different specialty clinics for a range of complications. They often receive almost continuous antibiotics for infections and are off work for long periods of time.

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Members of the consensus panel are given at the end of the article.

Summary points

● Lack of awareness of the range of primary antibody defects has resulted in considerable underdiagnosis and diagnostic delay

● Patients who receive an early diagnosis and appropriate immunoglobulin replacement therapy lead normal lives; those in whom the condition is undiagnosed have recurrent infections, often severe, as well as malabsorption, anaemia, or bronchiectasis—primary antibody deficiency is a costly diagnosis to miss

● Not all patients present with recurrent acute infections in childhood: failure to thrive, unexplained hepatosplenomegaly or arthropathy, and chronic infection are common presenting features, and over 95% of patients present as adults

● All patients should be referred to a consultant immunologist for precise diagnosis and long term management, often in conjunction with an appropriate specialist or paediatrician, or both

● Recent expansion of clinical immunology services allows opportunities for better patient care

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Types of primary antibody deficiencies

● **Common variable immune deficiency**
—Low serum IgG and IgA concentrations, including IgG subclasses, with or without low serum IgM levels

● **X linked antibody deficiency**
—Occurs in boys before the age of 2 years
—Some have a family history

● **IgG subclass deficiencies**
—May be an indication for immunoglobulin replacement therapy in patients with recurrent infections who also do not produce specific IgG antibodies after test immunisations

● **Specific antibody deficiency**
—Occurs in patients with a classic history of humoral immune deficiency who fail to respond to test immunisations, despite having normal serum concentrations of total IgG, IgA, IgM, and IgG subclasses

● **Selective IgA deficiency**
—Occurs in 1 in 700 of population
—Many affected people may be symptom free, particularly if deficiency is discovered by chance
—Patients with the deficiency who have recurrent infections may also have an underlying deficiency in a subclass of IgG or specific antibody

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Immunoglobulin replacement therapy obviates most of these complications[7]—primary antibody deficiency is a costly diagnosis to miss.

The term primary antibody deficiency has been expanded to include several types of deficiencies, of which common variable immune deficiency[1] is the most widespread. According to Swedish data on prevalence,[8] there should be around 2500 such patients in the United Kingdom,[9] but the British register for primary immune deficiencies currently records less than 1000 such patients.[10] Furthermore, a survey in the North West region showed that the average diagnostic delay for common variable immune deficiency was 2·5 years in children and 5·5 years in adults,[11] which shows the poor awareness of this condition. As few as 1 in 4 hospital consultants and 1 in 15 general practitioners probably have a patient with the condition on their list.

A common reason for this lack of awareness in adults is the widespread but erroneous belief that all primary immune deficiencies present in childhood. Ninety five per cent of patients with common variable immune deficiency present after the age of 6 years.[5] Diagnostic delay results in unnecessary morbidity from untreated

> **Indicators of primary antibody deficiencies**
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> ● Unexplained failure to thrive
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> ● Excess of infections
> —Recurrent infections at different sites, or even within a single system, requiring frequent prescription of antibiotics
> —Particularly severe, unusual or persistent infections (such as bronchiectasis) even if serum immunoglobulin concentrations are normal
> —Need for intervention for chronic infections such as tonsillitis, otitis media, or recurrent boils
> —Need for instigation of second line tests for chronic infection—for example, sweat tests or ciliary beat measurements
>
> ● Abnormal lymphoid tissue, such as nodular lymphoid hyperplasia in the gut or congenital absence of tonsils
>
> ● Unexplained signs such as hepatosplenomegaly or arthropathy

disease and makes patients with complications from longstanding primary antibody immunodeficiency difficult to manage. Confusion with HIV disease has caused considerable distress in many patients.

The scarcity of clinical immunology services in the past has resulted in many patients being managed in centres where only a few patients with antibody deficiencies are seen. As a result of this lack of experience, the management of some patients has been inadequate, to say the least. With the recent expansion of clinical immunology services, the availability of services has become more widespread and immunological advice is given more quickly, resulting in opportunities for better patient care.

As a result of an initiative from the patient support society, the Primary Immunodeficiency Association, a group of physicians, paediatricians, and specialists in related disciplines, met with nominated representatives from the Royal College of General Practitioners, Royal College of Nursing, and a consultant in Public Health Medicine (for purchasers) to develop consensus guidelines for the diagnosis and management of primary antibody deficiencies.

Whom to test?

Clinical history is the most important aspect of suspecting a diagnosis of primary antibody deficiencies. Failure of antibody production results in reduced host defence to pathogens, particularly bacteria; many patients therefore present with recurrent infections due to a wide range of common organisms. These infections may not necessarily be life threatening and are often quite mild, responding normally to oral antibiotics. Not all patients present with recurrent infections; the box shows the clinical clues that should raise suspicions of immune deficiency so that the appropriate tests may be performed.

How to diagnose?

All patients in whom there is a definite or suspected antibody defect should be referred to a specialist clinical immunologist. Since antibody deficiencies are uncommon, there is a need for considerable clinical experience in interpreting the tests as well as in assessing the clinical history.

When serum immunoglobulin concentrations are greatly depressed confirmatory tests are not always necessary. However, patients with serum IgG concentrations in the low part of the normal range and a history of recurrent infections require investigation (box). Confirmatory tests, such as the absence of specific antibodies following both immunisations and infections (to which the patient is known to have been

exposed), are required. Interpretation of poor or suboptimal immunisation responses requires in depth training and skill, and these assays should be performed only in specialist centres. Measurements of IgG subclasses, like serum immunoglobulin concentrations, are related to the normal range for age. It is important not only to measure antibody responses to test immunisation but also to assess the extent of concurrent T cell deficiency.

In addition to their immunological assessment, patients should have investigations to identify the degree of long term damage present at the start of treatment to provide a baseline against which the efficacy of treatment can be monitored.

Role of specialists in clinical immunology

Patients must have a full immunological assessment before starting immunoglobulin treatment. This is best done by referral to their nearest clinical immunologist. With the expansion of clinical immunology centres in the past decade, specialist care is readily available in most regions of the United Kingdom (appendix). Most patients will require treatment. However, some patients gradually develop antibody deficiency over several years and patients with a classic history of immunodeficiency who have normal results at their initial investigation therefore require specialist follow up and may need replacement therapy several years later. Likewise, patients with low immunoglobulin concentrations detected by chance should also be followed up as most such patients develop symptoms eventually and require replacement therapy.

Most consultant immunologists prefer to start immunoglobulin replacement therapy in their own centre, where specialist immunology nurses can help with the management and education of the patients and their relatives. The choice of immunoglobulin therapy, both product and route of administration, is complex. Clinical immunologists are familiar with the range of products and their availability, so that replacement therapy can be tailored to individual patient needs. A high proportion of patients can join a recognised self infusion immunoglobulin programme (see appendix).[12] After formal training in a recognised centre patients are monitored by the consultant immunologist every three to six months. Those whose cases are unsuitable may be referred to their local hospital for maintenance immunoglobulin replacement therapy, which will be supervised by a nurse specialising in immunology; the treatment of these patients is also assessed regularly in the consultant immunologist's clinic.

Clinical immunologists need to continue to review all patients as outpatients every three to six months to assess progress and to detect possible complications.

> **How to diagnose primary antibody deficiencies**
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> All patients who have or are suspected of having an antibody defect should be referred to a specialist immunologist, who will usually measure:
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> ● Serum immunoglobulin concentrations in relation to normal ranges for age
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> ● Test immunisations: antibody responses (IgG) to proteins and carbohydrate vaccines
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> ● Existing antibody (IgG) responses to previous infections
>
> ● Existing antibody (IgG) responses to previous known immunisations
>
> ● IgG subclasses related to normal ranges for age
>
> ● Lymphocyte subpopulations concerned with antibody production

Patients with chronic chest or gastrointestinal disease also need continued advice from their chest physician or gastroenterologist. Shared care between immunologists and local physicians or paediatricians may be necessary, especially if the patient lives a long way from the immunology centre; shared care with the general practitioner is essential. Patient or parent held records are recommended to ensure good communication (these are not a substitute for doctors' records).

Aims of management

The aims of management, which are largely the same in adults and children, are to prevent the onset of complications and to enable a normal working capability and life expectancy, and in children to ensure optimal growth and development (box). Patients require replacement immunoglobulin; this is available in three forms, depending on whether it is given intravenously, intramuscularly, or subcutaneously.

Immunoglobulin replacement therapy

The efficacy of immunoglobulin was originally shown in the Medical Research Council trial (1955-70) of intramuscular immunoglobulin. Since then intravenous immunoglobulin has been shown to be the treatment of choice since trials showed that higher doses of intravenous immunoglobulin were more effective.[13]

Once the preparation and its route of administration have been selected for a patient, the minimal risks of viral transmission and possible adverse reactions to immunoglobulin therapy should be discussed with the patient. He or she should also be given an opportunity to discuss the treatment with a patient who has experienced similar immunoglobulin replacement. Liver transaminase concentrations, serum creatinine concentration, and anti-IgA antibody titres (if indicated) should be measured as baseline. On the day of infusion overt active infection should be excluded as immunoglobulin infusions during an acute infection may result in serious adverse reactions.

The dose of intravenous immunoglobulin required is initially determined by the severity and frequency of infections as well as the serum IgG concentration. Most patients receive about 400 mg/kg/month, usually in two doses, two weeks apart, since the half life is 3 weeks[7]; very few require doses of 1 g/kg/month in divided doses.[13]

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin is the preferred treatment for most patients with antibody deficiencies. The World Health Organisation has produced criteria for the production of suitable preparations.[14] Each is the product of a different manufacturing process so that products are not interchangeable. Indiscriminate use of more than one product in a given patient will prevent identification of the source of hepatitis C or other transmissible agent if such an infection occurs.

Adverse reactions are mostly related to infusion rates. The first few intravenous infusions should be given very slowly, with antihistamine and hydrocortisone available. Adrenaline should always be available, even at home, in case of anaphylaxis. Adverse reactions may be mild, moderate, or severe.[15] In some patients symptoms, particularly headaches or abdominal pain, may be delayed for up to 24 hours after an infusion. In rare cases patients may develop antibodies to IgA after infusion of blood, plasma, or immunoglobulin containing IgA.[16] IgA free material should be used for patients with very high or rising titres of IgA antibodies.[17]

> ## Aims of management
> ● To prevent further acute infections
> ● To halt the progress of complications if present
> ● To reverse previous damage when possible
> ● To recognise further complications early and manage them, particularly those not amenable to replacement immunoglobulin therapy
> ● To avoid complications of replacement immunoglobulin therapy
> ● To develop approaches to management, based on individual needs, for the lifelong replacement of immunoglobulin, including self administration when possible
> ● To encourage greater participation of patients in the management of their disease
> ● To ensure good liaison with patients and all their medical advisers

Regular follow up by a clinical immunologist is essential; in patients with specific complications shared care with an appropriate specialist is necessary.

INTRAMUSCULAR IMMUNOGLOBULIN

Intramuscular immunoglobulin is now largely superseded by intravenous immunoglobulin. Although transmission of infectious agents, including hepatitis viruses, by intramuscular immunoglobulin has not been reported, the risk of an immediate adverse reaction is considerable; up to a fifth of patients have a reaction at some time, and these reactions may be severe (anaphylactoid).

RAPID SUBCUTANEOUS IMMUNOGLOBULIN

Some intramuscular and intravenous immunoglobulins may be given subcutaneously. Rapid subcutaneous immunoglobulin infusions are still at an early stage of use in the United Kingdom, though there is considerable experience in adults in Sweden.[18] A European collaborative group is investigating the use of such infusions in children. A multicentre study is also underway in Europe to compare the efficacy with that of intravenous immunoglobulin in adults.

TRANSMISSION OF VIRUSES

To date no immunoglobulin preparation has been found to transmit retroviral infection, probably because this group of viruses is destroyed by cold ethanol during manufacture.[19] Several preparations, however, have been associated with outbreaks of non-A, non-B hepatitis; such transmission was related to particular batches of intraveous immunoglobulin.[20] Since fractionation does not completely inactivate or eliminate this group of viruses, the transmission of non-A, non-B (including hepatitis C) viruses is probably a result of the size of the inoculum. To prevent contaminated donations being used all manufacturers are now required to test all donations for hepatitis C antibodies as well as HIV antibodies and hepatitis B surface antigen. The manufacture of some intravenous immunoglobulins includes heat treatment or the addition of detergent specifically to inactivate viruses. Batch numbers of all preparations infused into individual patients must be recorded to enable the contaminated batch to be traced if viral transmission occurs.

Complications of primary antibody deficiencies
ACUTE INFECTIONS

Despite adequate immunoglobulin treatment breakthrough infections may occur. They should be treated quickly with appropriate antibiotics at the maximum dose and for longer than in immunocompetent

patients. Prophylactic antibiotics should be given only after consultation with the organ based specialist and others concerned with the patient's care. Unusual organisms such as mycoplasmas, which are difficult to culture, may be the cause of infection.

LONG TERM COMPLICATIONS

Chronic disease may be associated with the natural course of the condition, delayed diagnosis, or inadequate treatment.[26] Long term complications are listed in the box.

Patients with persistent purulent sputum should be assessed and managed jointly with a chest physician to prevent progressive lung damage and to monitor functional impairment.[8] Meticulous attention to postural physiotherapy, antibiotics, bronchodilators, and local anti-inflammatory agents is needed if insidious progression of lung damage is to be arrested. Discrete pulmonary shadows may be due to granulomas, and the patient may not require treatment; symptomatic lesions may respond to oral corticosteroids. Patients with antibody deficiencies, as well as their families, should not smoke.

Adults often present with recurrent sinusitis. A full otorhinolaryngological assessment (including nasendoscopy and computed tomography) is needed; local treatment of the nose may decrease the frequency of infections. When diarrhoea and malabsorption are recurrent or persistent several, careful attempts should be made to detect a pathogen in the stool. Endoscopy may be needed to obtain appropriate biopsy specimens, which should always be stained for specific pathogens —for example, giardia or cryptosporidia. Abnormal results in liver function tests may reflect naturally or iatrogenically acquired hepatitis.

Septic arthropathy may present insidiously. Chronic arthropathy or arthralgia is often sterile, transient, and usually related to infection elsewhere, suggesting a cause related to the immune complex. In a few patients it may be persistent, especially if diagnosis and treatment have been delayed.

Anaemia is common and may be due to iron deficiency or chronic illness. Iron deficiency anaemia is more common in patients with diarrhoea or atrophic gastritis. Unexplained persistent, non-troublesome splenomegaly occurs in 30% of patients. The only indications for splenectomy, which should be avoided if possible in view of the additional risk of infection, are persistent and life threatening idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia, and clinical hypersplenism. If lymphoma is suspected for other reasons, biopsy is necessary, particularly as patients with common variable immune deficiency have an increased risk of lymphoma.[26]

Awareness of primary antibody deficiencies

Increasing the patient's understanding of the disease is an important component of management. Patients should be made aware of the Primary Immunodeficiency Association and invited to receive relevant publications. The nationwide survey of consultants recently completed by the association should increase awareness among the medical profession.

Awareness of these conditions has been highlighted by recent advances in determining the genes in those antibody defects which are inherited. These are often, but not exclusively, X linked conditions in which early development of B cells is abnormal[21] or in which the ligands for T and B cell cooperation are abnormal.[22] The contribution of the patients and their families to the understanding of the physiology of antibody production is recognised.

Conclusions

The range of primary antibody defects includes common variable immune deficiency in children and adults, X linked antibody deficiencies in male infants, and deficiencies of IgG subclasses and specific antibodies in patients with recurrent infections. Lack of awareness has resulted in underdiagnosis and diagnostic delay; these diseases should be considered more widely.

Recent expansion of clinical immunology services allows opportunities for better patient care. In view of the wide range of complications, all patients with primary antibody deficiencies should be managed by a clinical immunologist, often in conjunction with another specialist.

Long term complications of primary antibody deficiencies

Chest
- Bronchiectasis
- Fungal infections (rarely)
- Polyclonal lymphoid aggregates
- Granulomas
- Lymphoma

Sinuses
- Recurrent sinusitis

Gut
- Infections (giardia, cryptosporidia)
- Malabsorption
- Superinfection
- Autoimmune enteropathy
- Sclerosing cholangitis
- Atrophic gastritis
- Food sensitive enteropathy
- Colitis
- Gastric carcinoma

Liver
- Naturally acquired hepatitis
- Associated autoimmune diseases (chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis)
- Non-infective granulomas

Joints
- Septic arthropathy
- Chronic sterile arthropathy and/or arthralgia

Blood
- Autoimmune haemolytic anaemia
- Immune thrombocytopenic purpura
- Iron deficiency anaemia
- Anaemia of chronic illness
- Aplastic anaemia

Brain
- Acute enteroviral meningoencephalitis
- Chronic cerebral granulomas

Spleen
- Unexplained splenomegaly in 30%

Eyes
- Keratoconjunctivitis
- Uveitis

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Appendix

Immunology centres for specialist diagnosis and management of primary antibody deficiencies (*home treatment centre)

East Anglia
Cambridge—Addenbrooke's Hospital (Drs D Brown and P Ewan)

London
Specialist Children's Centre—Great Ormond Street Hospital* (Drs G Morgan and S Strobel)
South West Thames—St George's Hospital* (Drs S Pereira (adults) and G Davies (children))
North East Thames—Royal Free Hospital* (Dr D Webster)

Oxford
Oxford—John Radcliffe Hospital* (Drs H Chapel and G Bird)

Northern and Mersey
Newcastle—Newcastle General Hospital* (Drs A Fay and G Spickett (adults) and A Cant (children))

North West
Salford—Hope Hospital* (Dr M Haeney)
Manchester—Manchester Royal Infirmary (Dr R Pumphrey)

South West
Bristol—Southmead Hospital (Dr T Wallington)

Trent
Nottingham—Queen's Medical Centre* (Professor H Sewell)
Leicester—Leicester Royal Infirmary (Professor K Whaley)

Wessex
Nearest centres: Bristol and Oxford

West Midlands
East Birmingham Hospital—Birmingham Heartlands Hospital* (Professor R Thompson)

Dudley Road Hospital—Dudley Road Hospital (Dr D Kumararatne)

Yorkshire
Leeds—St James Hospital (Dr Gooi)

Wales
Nearest centres: Birmingham, Bristol, Salford, and Oxford

Scottish Health Boards
Edinburgh—Edinburgh Royal Infirmary (Dr P L Yap)
Glasgow—Glasgow Royal Infirmary (Dr A Farrell)

Northern Ireland
Belfast—Royal Victoria Hospital* (Dr D McCluskey)

Republic of Ireland
Dublin—St James's Hospital (Professor C Feighery)

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ANY QUESTIONS

"Active neurological disease" is regarded as a contraindication to influenza vaccination in one manufacturer's leaflet. Does having an abnormal electroencephalogram or a history of epilepsy constitute an active neurological disease?

Four preparations of influenza vaccine are available in Britain. Neurological conditions are mentioned in the product insert of only one, which is produced in North America. Inquiries to the manufacturers revealed that they define an active neurological disorder as "a disorder that is yet to be identified or stabilised." An abnormal electroencephalogram or a history of epilepsy by itself would not fall into this definition. Poorly controlled epilepsy, on the other hand, would. In such patients it might be prudent to use an alternative to this particular brand.

There is no evidence, however, that any influenza vaccine, if given to someone with an active neurological disorder, would give rise to a deterioration in the condition or an increased risk of any adverse reactions. The fact that the vaccine is produced in North America may be relevant to what would seem to be an overcautious recommendation.—DAVID ELLIMAN, *consultant in community child health, London*