Primary antibody deficiency and diagnostic delay

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Consider primary antibody deficiency in patients with repeated infections

The prevalence of primary antibody deficiency is at least 1-2/50 000 population.[1] By far the commonest presentation is recurrent pyogenic bacterial infection of upper and lower respiratory tracts, although some patients also develop meningitis, septicaemia, diarrhoea, skin infection, osteomyelitis, or arthritis.[2] Failure to diagnose the condition causes considerable morbidity, particularly progressive chronic lung disease.[1] Since most types of primary antibody deficiency can be diagnosed readily and treated successfully, underlying antibody deficiency should be considered as a possible diagnosis in any patient, of any age, whose infections are more persistent or more severe or recur more frequently than those in other members of that peer group.

We reviewed the clinical presentations of patients with primary antibody deficiency from north west England to determine whether the diagnosis was made promptly or delayed and, when it was delayed, to analyse whether the delay contributed to morbidity.

Patients and methods

The case histories of 31 patients (16 children and 15 adults) with primary antibody deficiency were reviewed and all major and minor infections that occurred before diagnosis were noted.

Patients with antibody deficiency included those with X linked hypogammaglobulinaemia, common variable immunodeficiency, or IgG_2 subclass deficiency. X linked hypogammaglobulinaemia (Bruton's disease) was diagnosed according to World Health Organisation criteria[3]: male patient; onset of disease in infancy or early childhood; serum IgG concentration below 2·0 g/l, with appreciably decreased IgA and IgM concentrations for age; absence of functional antibodies; normal cell mediated immunity; and pre-B lymphocytes in the bone marrow but no mature B cells in peripheral blood.

Common variable or late onset immunodeficiency comprises a heterogenous group of disorders, usually characterised[3] by hypogammaglobulinaemia (serum IgG concentration below 2·0 g/l), impaired antibody synthesis, combined B and T lymphocyte immaturity or lymphopenia, no clear cut pattern of inheritance, and onset of symptoms at any age but especially at 30-40 years.

Selective IgG_2 subclass deficiency was defined as an IgG_2 subclass concentration more than two standard deviations below the normal age matched mean and a poor antibody response to immunisation with pneumococcal polysaccharide antigens in a patient with a history of repeated bacterial sinopulmonary infections.[4]

Patients whose hypogammaglobulinaemia was caused by protein loss, drugs, prematurity, malignancy, or infection were excluded.

Using a modified infection scoring system (see box[5]) we gave scores of 10 to major infections and 5 to minor infections. We arbitrarily defined diagnostic delay as a failure to suspect the possibility of antibody deficiency when the patient's infection score exceeded 25 points (equivalent to two major and one minor infection or one major and three minor infections) over three years. A morbidity score was derived from the number of infections experienced subsequently, in the interval before the diagnosis was made and treatment started.

Major infection *(requiring admission to hospital)*	**Minor infection**
Score=10	*Score=5*
Pneumonia	Otitis media
Meningitis	Bronchitis
Septicaemia	Pleurisy
Septic arthritis	Skin sepsis

Scoring system used to assess need for investigation of antibody deficiency

Results

Diagnostic delays were found in 14 of the 15 adults and eight of the 16 children with primary antibody deficiency (table). The median duration of delay was 5·5 years in adults (range 2-27 years) and 2·5 years in children (range 1-5 years). As a result of this delay the median morbidity score in adults was 40 (range 15-80), equivalent to a further four major infections before the diagnosis was made. In children the median morbidity score was 37·5 (range 15-90).

Of the 22 patients who suffered diagnostic delay the commonest reason (17 cases) was straightforward failure to recognise the clinical syndrome of antibody deficiency. In three of these patients hypogammaglobulinaemia had been noted previously but the importance of the laboratory result had either been ignored or not been appreciated, and adequate immunoglobulin prophylaxis had not been given. In the remaining five patients delay was due mainly to a failure to recognise the recently reported syndrome of IgG_2 subclass deficiency.[4]

In general paediatricians had a higher index of suspicion than adult physicians and thus delays in children were shorter, particularly in inherited forms of antibody deficiency. Of the six boys with X linked hypogammaglobulinaemia in whom there was no diagnostic delay four were younger brothers of the two boys with a delayed diagnosis. Delay seemed especially likely when individuals were referred to organ based specialties. Seven of the 22 patients presented repeatedly with otitis media to ear, nose, and throat departments, where their histories of infections at other sites tended to be overlooked.

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Length of diagnostic delay and morbidity scores in adults and children with primary antibody deficiency

Group	No delay	Delay	Length of delay (median (range) or actual delay (years))	Morbidity scores (median (range) or actual scores)
Adults (n=15)	1	14	5·5 (2-27)	40 (15-80)
X linked hypogammaglobulinaemia	0	0		
Common variable immunodeficiency	1	12	6·5 (2-27)	47 (15-80)
IgG_2 subclass deficiency	0	2	3, 6	20,30
Children (n=16)	8	8	2·5 (1-5)	37·5 (15-90)
X linked hypogammaglobulinaemia	6	2	3,3	35,40
Common variable immunodeficiency	2	3	1, 3, 5	15, 45, 90
IgG_2 subclass deficiency	0	3	1, 1, 2	20, 25,50

Discussion

Despite the general availability of immunological diagnostic techniques, antibody deficiency continues to be diagnosed late and in many patients after irreversible structural lung damage has occurred. There is still widespread ignorance about the importance of major immunoglobulin deficiencies and their association with recurrent bacterial infections, particularly in adults with common variable immunodeficiency. The reported prevalence of hypogammaglobulinaemia[1 6] is generally accepted to be an underestimate, and failure to diagnose the condition is probably partly responsible for the differences in the prevalence of hypogammaglobulinaemia between European countries and even between regions of these countries.

The most common presentation of antibody deficiency is recurrent sinopulmonary infection. Most adults accept as normal small amounts of mucopurulent sputum, and this may contribute to the considerable delay between the onset of symptoms easily identified by the patient and diagnosis. Delayed diagnosis or inadequate immunoglobulin replacement results in significant impairment of lung function and body growth.[1] Since early diagnosis and efficient immunoglobulin prophylaxis,[7] supported by antibodies when necessary, can prevent the progression to chronic disabling lung disease, it is essential to exclude the diagnosis of antibody deficiency early in the investigation of any patient with repeated bacterial infections.

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