Primary antibody deficiency and diagnostic delay

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Methods: A retrospective case note review was performed of 89 consecutive patients with antibody deficiency referred to a regional referral centre for clinical immunology in northwest England and north Wales. The delay in diagnosis and the estimated resulting morbidity in terms of infections were assessed.

Results: Fifty six of the 89 patients experienced delay in diagnosis. The overall median delay was 2 years (mean, 4.4), resulting in substantial morbidity (equivalent to two major infections and one minor infection). This shows a moderate improvement since the previous study in 1989 and since the introduction of UK national guidelines in 1995. Respiratory infections are the most frequent presenting infections, and respiratory physicians the most common source of referral.

Conclusions: There is still considerable delay in the diagnosis of primary antibody deficiency, but the data suggest an improvement in practice since the previous study in 1989 and the distribution of national guidelines in 1995.

Primary antibody deficiency comprises a group of innate and acquired immunological disorders characterised by failure to produce adequate circulating antibodies, with resulting susceptibility to bacterial and other infections. These disorders were originally recognised 50 years ago after the development of electrophoretic techniques that allowed the semiquantitative analysis of serum immunoglobulins. The most prevalent important defect is common variable immunodeficiency, characterised by greatly reduced serum concentrations of IgG and IgA and sometimes IgM. Functional antibody deficiency has been recognised more recently, and is characterised by low concentrations of circulating antibodies to pneumococcal or haemophilus antigens (with normal total IgG serum concentrations) and failure to mount an adequate response after infection or vaccination, in addition to IgG2 subclass deficiency. These disorders can present at any age with no recognised sex preponderance. X linked agammaglobulinaemia (XLA; Bruton’s disease), presents in boys, typically between the ages of 4 months and 2 years, and is usually diagnosed in paediatric practice.

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The different causes of primary antibody deficiency share a similar clinical phenotype, characterised by recurrent bacterial infections. About 90% of patients present with recurrent respiratory tract infections, often leading to bronchiectasis, although other common infections include gastrointestinal, meningeal, joint, bone, and skin.

Early diagnosis of antibody deficiency is important because morbidity and mortality are high and the efficacy of immunoglobulin replacement treatment is well established.

We have previously shown considerable delay in the diagnosis of antibody deficiency in patients from north west England, with a median delay of 5.5 years in adults and 2.5 years in children. Several other studies have confirmed this finding, based on the time of initial symptoms until the time of diagnosis. A UK national audit led to recommendations on early diagnosis that were distributed to all UK general medical practitioners and specialist clinicians to whom patients with antibody deficiency are most commonly referred.

The aim of our study was to reassess the impact of such recommendations on diagnostic delay in patients referred to clinical immunology services at our hospital since our previous study.

METHODS

We reviewed the case histories of 89 consecutive patients referred to the immunology clinic with antibody deficiency between 1989 and 2002. Hope Hospital, Salford is a regional referral centre for adult patients with primary immunodeficiency disorders from north west England and north Wales.

Diagnosis was based on the combination of accepted clinical and laboratory criteria. Common variable immunodeficiency was based on very low total serum IgG and IgA values (at least 2 SD below the mean for age), poor antibody responses to vaccines, onset of antibody deficiency over 2 years of age, and the exclusion of other defined causes of hypogammaglobulinaemia. XLA was defined as a male patient with <2% of CD19 positive B cells in the blood, a btk mutation, maternal history of XLA, serum concentrations of IgG, IgA, and IgM more than 2 SD below the mean for age, and onset of recurrent bacterial infections in the first 2 years of life. Selective IgG2 subclass deficiency was diagnosed on the basis of an IgG2 subclass concentration at least 2 SD below the normal age corrected mean, in addition to a poor antibody response to immunisation with pneumococcal polysaccharide vaccine in a patient with a history of repeated bacterial sinopulmonary infections. The diagnosis of functional antibody deficiency was based on significantly reduced concentrations of pneumococcal or haemophilus antibodies of IgG isotype before and after immunisation with the relevant vaccine in a patient with relatively preserved serum immunoglobulin concentrations and a history of repeated bacterial sinopulmonary infections. Patients for whom there was incomplete information to assess the history of infections reliably were excluded. We also excluded patients...
with hypogammaglobulinaemia as a result of drugs, protein losing enteropathy or nephropathy, bone marrow transplantation, malignancy, or immunodeficiency associated with thymoma (Goods syndrome).

As previously reported, we used a modified infection scoring system (table 1) to measure diagnostic delay and morbidity. We arbitrarily defined diagnostic delay as a failure to suspect antibody deficiency when the patient’s infection score reached 25 points or more in a three year period. Morbidity was defined as the total number of additional points accumulated from the time the diagnosis should have been suspected until the time the diagnosis was made.

RESULTS
The mean age of the patient group at presentation was 41 years (range, 6–71). There were 57 patients with common variable immunodeficiency, 28 patients with functional antibody deficiency, three patients with IgG2 subclass deficiency, and one patient with XLA.

Diagnostic delay was found in 56 of 87 patients. Across all patients, the median duration of diagnostic delay was 2 years with a mean of 4.4 years (range, 0–41). As a result of this delay, the median accumulated morbidity score was 25 points and the mean was 43 points (range, 0–250).

We also compared diagnostic delay in patients diagnosed before and after the distribution of national guidelines on the diagnosis of antibody deficiency. For the period 1989–1995, the median diagnostic delay was 3.5 years (mean, 6.2) with an associated median morbidity score of 42 points (mean, 47). For patients diagnosed between 1996 and 2002, the median diagnostic delay was 1 year (mean, 3.5) with a median morbidity score of 25 points (mean, 43). This difference in diagnostic delay approached significance (p = 0.052; one tailed t test).

The most common presenting symptom was respiratory tract infection (78 of 89), with pneumonia requiring hospital treatment occurring in 33 of 89 and bronchiectasis (diagnosed on computerised tomography scan) in 18 of 89 patients. Otitis occurred in 16 patients, sinusitis in 17, gastroenteritis in six, meningitis in two, osteomyelitis in one, and septic arthritis in one. The most common sources of referral to our clinic were respiratory physicians (36%), general physicians (19%), haematologists (13%), paediatricians (10%), and general practitioners (6%), with specialists in infectious diseases, gastroenterology, rheumatology, neurology, and ear, nose, and throat surgery accounting for 16% of referrals.

DISCUSSION
Despite the widespread availability of immunological diagnostic methods, these data support the hypothesis that there remains a considerable delay in the diagnosis of primary antibody deficiency. We found a delay in 56 of the 87 (64%) patients in our present study, compared with 71% in our previous study. If patients with XLA are excluded, then diagnostic delay was found in 66% of adults compared with 93% previously.

The median delay in diagnosis of two years and median morbidity score of 25 points compares favourably with our previously reported delay of 5.5 years in adults and morbidity score of 40 points. Overall, the data suggest an improvement in practice over the past 14 years. The data for the period 1989–1995 and 1996–2002 suggest a further more recent improvement, possibly related to the distribution of UK national guidance in 1995. Nevertheless, the median morbidity score of 25 points, equivalent to two major infections requiring hospital admissions plus one minor infection, highlights the clinical consequences of suboptimal diagnosis. For one patient, the morbidity score reached 250 points before diagnosis was reached.

“The low proportion of referrals from general practitioners is surprising”

The data confirm the typical profile of infections seen in antibody deficiency, with recurrent respiratory tract infection being the most common. Correspondingly, chest and general physicians would be expected to be a common referral source, although the low proportion of referrals from general practitioners is surprising. This may reflect continued low awareness in primary care of the condition, even though immunoglobulin measurement is widely available and inexpensive.

In conclusion, there remains considerable delay in the diagnosis of primary antibody deficiency but the data suggest an improvement in practice since our previous study.

Take home messages
• Our results suggest that there is still a considerable delay in the diagnosis of primary antibody deficiency, resulting in substantial morbidity (equivalent to two major infections and one minor infection)
• However, there has been an improvement in practice since our previous study in 1989 and also since the distribution of national guidelines in 1995

Table 1 Scoring system for infections

<table>
<thead>
<tr>
<th>Minor infection (examples of infections not requiring hospital admission)</th>
<th>Score = 5 points</th>
<th>Major infection (examples of infections requiring hospital admission)</th>
<th>Score = 10 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest infection requiring antibiotics</td>
<td>Pneumonia</td>
<td>Sinusitis</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Otitis</td>
<td>Osteomyelitis</td>
<td>Gastroenteritis</td>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Skin sepsis</td>
<td>Septicemia</td>
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REFERENCES