Quality Improvement Report

Management of primary antibody deficiency by consultant immunologists in the United Kingdom: a paradigm for other rare diseases

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Abstract

Variation in clinical practice and its effect on outcome is little known for rare diseases such as primary antibody deficiency. As part of a national audit, a survey of all 30 consultant immunologists in the United Kingdom dealing with primary antibody deficiency syndromes in adults and children was carried out in 1993 to ascertain their practices in diagnosis and management. Consensus guidelines were published after the survey was completed. Comparison of the survey results of clinical practice at the time the guidelines were published with the standards identified highlighted that the practice of a minority of specialists was at variance with their peers and with the consensus document, particularly in the use of intramuscular immunoglobulin, the dose and frequency of intravenous immunoglobulin, and target trough immunoglobulin G concentration, which has implications for the quality of patient care. However, much closer agreement existed in the key areas of management, such as diagnosis and selection of intravenous immunoglobulin. The approach and the problems identified are relevant to the management of other rare diseases, in which diagnosis and management is complex and there are few specialists with the necessary knowledge to undertake such care. This survey, the first attempted audit of practice, shows that within a motivated group of specialists highly significant differences in practice may exist, and the authors emphasise the importance of setting clear guidelines against which care can be assessed.

(Keywords: primary antibody deficiency, guidelines, audit)

Introduction

Little information exists on how quality of specialist services for patients with rare diseases can be assessed and how variations in that care offered may affect clinical outcome.

Not all patients are managed by consultants with a special interest in primary immunodeficiencies; some patients are managed by paediatricians, haematologists, and other physicians. Published work gives no clear guidance on the optimum management of such patients, other than to point to certain minimum standards. A medical panel convened by the Primary Immunodeficiency Association produced a consensus document in 1994 on the management of such disorders, which is summarised in the following box.

As part of a national audit of the quality of care received by patients with antibody deficiency, it was thought to be important to ascertain the views of the immunologists managing such patients and to compare existing practice with the standards in the consensus document. If specialists with a particular interest in these conditions are not agreed on the optimum approach then it will be difficult to convince non-specialists of the correct management approach. The problems
Major recommendations of consensus document on management of primary antibody deficiency

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

2. The following investigations should be carried out: serum immunoglobulins, in relation to normal range for age, existing immunoglobulin G responses to previous infections and immunisations, test immunisation with protein and polysaccharide antigens (immunoglobulin G), immunoglobulin G subclasses related to normal ranges for age and lymphocyte subpopulations. Long term tissue damage should be documented and investigated before treatment.

3. Patients are likely to require doses of intravenous immunoglobulin between 0-4-1 g/kg/month, given in divided doses, usually two weeks apart, since the half life of immunoglobulin G is three weeks. Intramuscular immunoglobulin is now largely superseded.

4. Patients should be considered for home treatment programmes; those unsuitable should have their infusions in their local hospital supervised by a nurse specialising in immunology.

5. All patients should be reviewed every 3-6 months by a consultant immunologist for adequacy of treatment and development of complications.

6. Patients should be made aware of the Primary Immunodeficiency Association and invited to receive relevant literature.

7. The consensus document also lists recognised centres for specialist diagnosis and management and those centres providing approved training for home treatment.

Subjects and methods

We sent a questionnaire to all consultant immunologists thought to be involved in the care of patients with primary antibody deficiency. The selection was based on our personal knowledge of the interests and workload of the consultants; those who did not specialise in the care of patients with antibody deficiency were not circulated. The survey was not anonymous. The questionnaire contained specific questions about diagnosis and management of antibody deficiency syndromes, and respondents were asked to tick boxes to indicate their views to specific questions. The box shows an abbreviated form of the questions.

Information sought in questionnaire

1. Do you have direct responsibility for the care of patients with primary antibody deficiency?  
2. If no, do you advise other clinicians on managing patients with primary antibody deficiency?  
3. For a newly presenting adult patient with suspected antibody deficiency which investigations would you request on all patients (measurement of immunoglobulins, immunoglobulin G subclasses, specific bacterial and antiviral antibodies, lymphocyte surface markers)?  
4. If the diagnosis is compatible with common variable immunodeficiency would you: use intramuscular immunoglobulin, intravenous immunoglobulin, either, or accept patient’s choice?  
5. For those using intramuscular immunoglobulin dose and frequency was requested.  
5a. Reasons for preferring intramuscular immunoglobulin over intravenous immunoglobulin  
5b. Information on intramuscular immunoglobulin product used  
6. Information on method of selection of an intravenous immunoglobulin product for a patient  
7. Do you believe that changes in intravenous immunoglobulin product are potentially hazardous/undesirable?  
8. Which products do you currently use (list of available products given)?  
9. Respondents were asked to rank 11 criteria used in the selection of an intravenous immunoglobulin product, see table  
10. Were respondents consulted over purchasing contracts for intravenous immunoglobulin, whether this adversely affected clinical management, and effect of changes in contracts on prescribing?  
11. Details of dose of intravenous immunoglobulin used, method of calculating dose, and target trough immunoglobulin G  
12. Frequency of intravenous immunoglobulin administration – either fixed (with interval) or variable  
13. Investigations carried out to assess adequacy of treatment

of the quality of care in such a group of life threatening rare diseases are applicable to other rare diseases, where access to specialist expertise is limited. The first problem for patients with a rare disease is correct diagnosis, either in primary or secondary care: for patients with antibody deficiency diagnosis is often long delayed. If patients get as far as specialist centres, what safeguards are there that they will receive optimum care? There are difficulties in organising audit among a group of specialists distributed the length and breadth of the United Kingdom, more so when published reports provide no clear guidance on absolute standards and those standards that are available are set by those involved in the audit. In 1993 we undertook a questionnaire survey of consultant immunologists to investigate the level of agreement on the correct approach to managing patients with a defined group of rare immunodeficiency disorders and to assess their quality of care. This approach may have implications for the investigation of the care of other rare disorders. In order to improve standards of care the participants were sent the results of the survey.
The questionnaire data were entered on to a computer database for analysis. In view of the small number of respondents, the analysis was carried out with simple descriptive statistics to evaluate the views of the group. The results were compared against the standards identified in the consensus document.

Results
In all, 30 questionnaires (100% response rate) were received from immunologists actively managing patients with rare diseases, although some prompting was required in two cases.

**Consultants’ Responsibilities**
Of the 30 respondents, 23 had direct responsibility for patients’ care, seven of whom also advised other clinicians on management; five respondents had no direct responsibility, four of whom advised other clinicians on management; and two gave no response. This means that some patients are not receiving regular review directly by a consultant immunologist, which is a standard of the consensus.

**Diagnostic Tests**
Respondents were asked to indicate which investigations they would carry out on all patients with a suspected diagnosis of antibody deficiency. The figure shows the results for the 28 respondents who had direct or indirect responsibility for patients. Although all consultants would measure immunoglobulins, other investigations were not always thought necessary. Only 19 measured lymphocyte surface markers, 17 specific antibacterial antibodies, and 14 antiviral antibodies, all of which are recommended in the consensus document. Some investigations listed may clearly be viewed as second line and carried out only in particular clinical instances.

**Treatment of Patients with Common Variable Immune Deficiency, X Linked Agammaglobulinaemia, Immunoglobulin G Subclass or Specific Antibody Deficiency with Infections**
In a patient with common variable immune deficiency 20 immunologists responded that they would immediately recommend the use of intravenous immunoglobulin; whereas two would use either intramuscular immunoglobulin or intravenous immunoglobulin and six would leave the choice to patients. Immunologists using intramuscular immunoglobulin would all use a loading schedule of either daily intramuscular immunoglobulin or a single intravenous dose. Despite there being three intramuscular immunoglobulin products on the market licensed for use in antibody deficiency and their uniformity the six users of intramuscular immunoglobulin would use only one type. Of major concern is the finding that four out of 28 respondents would be prepared to use intramuscular immunoglobulin if the patient was a child with X linked agammaglobulinaemia. General reasons given for choosing intramuscular immunoglobulin included its cost and quick administration. There was little agreement among the respondents on the optimum management of patients with symptomatic immunoglobulin G subclass or specific antibody deficiency: 11 would use intravenous immunoglobulin, one intramuscular immunoglobulin, and 12 continuous antibiotics. One would use no treatment at all.

**Home Treatment**
Eight respondents did not offer their patients the option of home treatment, even though there are considerable advantages to suitable patients. In four cases this was owing to a lack of local facilities, even though other centres are prepared to take on distant patients and many patients in home treatment programmes...
The specific venous treatment would have been the target trough immunoglobulin G concentration sought by those immunologists using this measure (range <4 g/l to >8 g/l (normal range for serum immunoglobulin G about 6–16 g/l)): some respondents specified more than one target level, presumably indicating that they set the target according to clinical status. It is of concern that six were using target immunoglobulin G concentrations >5 g/l, the desirable threshold in one published study. One immunologist viewed a trough level of <4 g/l as satisfactory despite this being less than 66% of the lower limit of normal. Three immunologists were using follow up intervals of four weeks or greater. Monitoring of treatment by trough immunoglobulin G concentrations was carried out by 25 immunologists, but only 17 regularly measured lung function, a useful marker of the overall adequacy of replacement; 16 immunologists asked patients to keep symptom diaries.

**Discussion**

This survey highlights the differences in approach to the management of rare group of conditions undertaken by a group of interested specialists and compares it with management standards identified in a multidisciplinary consensus. Although overall there was good agreement with the standards identified, a minority of specialists were offering care that deviated significantly from the agreed standards in a way that may prejudice the quality of care – for instance, by inappropriate use of intramuscular immunoglobulin, unduly low target concentration of immunoglobulin for treatment, and lack of specialist follow up. Patients will also be inconvenienced by lack of access to facilities for self treatment at home, lack of supportive information and information about a patient support society.

A problem with postal surveys is that they analyse “reported practice,” which may differ from actual practice. However, all the participants in this survey agreed to participate in an extensive project to obtain clinical and outcome information on patients with antibody deficiency. That project is nearing completion and will provide information, by centre, of the quality of patient care. The project involves a review of the case notes of all identified patients with antibody deficiency and is being carried out in conjunction with efforts to produce an up to date register of patients with all types of immune deficiencies (G P Spickett and T Askew, unpublished). An interim analysis carried out on 392 records shows that significant numbers of patients have chronic
Offering a treatment that is probably less than optimum: if they find that the outcome is satisfactory then the data need to be published and compared with existing data.

This survey has drawn attention to the difficulties of ensuring uniformity of treatment for rare diseases even between specialists. Although the approach taken by immunologists overall is generally uniform, there is minority whose practice is at variance with their peers. The problems of poor quality care will be highlighted by the other part of this audit project which entails collecting data on morbidity and mortality in antibody deficiency. Dealing with the problem of inadequate care of patients by non-specialists will be difficult until the specialists themselves have ensured compliance with all the standards of the consensus document. We hope that the feedback of the survey data to the participants will highlight to individual immunologists where their practice differs from that of their peers. This survey is the first attempt at auditing the clinical performance of immunologists, but there is no formal mechanism available to regular a national audit forum. The current project is funded only for a fixed period. The question of who sets standards of care for rare diseases and how they are monitored for appropriateness and for implementation has not been addressed in any systematic way but is worth study, as such diseases often involve expensive tertiary care.

By agreement, the consensus panel identified centres where it believes sufficient expertise exists, based on numbers of patients treated, to manage antibody deficiency effectively. However, this will not be effective in improving patient care unless purchasing authorities are prepared to take notice and direct their contracts accordingly. The NHS Executive has produced guidance on contracting for specialist services, but in many regions the recommendations are not fully implemented. Designation of specialist centres, with appropriate staffing and funding, is required to deal appropriately with rare and chronic diseases.

We thank all the immunologists who responded to the survey and were prepared to commit their practice to paper. This study forms part of a larger audit project, funded by the NHS Executive, and supported by the North of England Clinical Immunology Audit Group and the Association of Clinical Pathologists.