Clinical and Experimental Immunology EDITORIAL REVIEW doi:10.1111/j.1365-2249.2006.03126.x

Early indicators of immunodeficiency in adults and children: protocols for screening for primary immunological defects

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Summary

Early recognition of primary immunodeficiency is essential to reduce morbidity and mortality, and yet failure to recognize these conditions is still a major problem for clinicians around the world. The problem is that general practitioners, physicians and paediatricians lack familiarity with these rare disorders, and lack guidance regarding the appropriate use of immunological investigations. A working party from the European Society for Immunodeficiencies (ESID) has published screening protocols for these rare disorders, which aim to help select which tests should be done in which patients. The success of these proposals will depend on all immunologists disseminating this information in a format that is suitable for the busy generalist, who may not be familiar with these immunological tests and concepts. Laboratories should expect increasing requests for these screening investigations, and should make themselves familiar with these protocols so that appropriate second-line investigations can be arranged in a timely fashion. Speedy and effective communication between the laboratory and clinician is essential, and clinically interpreted reports are mandatory. Although these protocols are part of a screening process, their effectiveness in practice remains to be established, and further refinement will be required over time. The early involvement of the clinical immunologist in cases of suspected immunodeficiency is key.

Accepted for publication 4 May 2006
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With hindsight, a diagnosis of primary immunodeficiency is sadly all too obvious. In the 1980s, reports emerged about the unacceptable delay in diagnosis between the onset of recurrent infections and the recognition of immunodeficiency and the start of treatment [1]. In 1995, consensus guidelines for general practitioners, physicians and paediatricians were jointly published by the Royal College of Physicians, the Royal College of Pathologists and the Primary Immunodeficiency Association in an attempt to facilitate early recognition of these disorders [2]. In 2002 the diagnostic delay for primary antibody deficiency was reassessed, and the authors were pleased to report an improvement in the mean diagnostic delay compared to the 1989 study, but disappointment that the mean diagnostic delay was 4·4 years (median 2 years) [3]. Audit of the prevalence of primary immunodeficiency has shown that regions that do not have a clinically led immunology service fail to recognize significant immunodeficiencies, with subsequent patient morbidity and mortality caused by diagnostic delay [4].

The proposals by de Vries *et al*. in this issue of *Clinical & Experimental Immunology* [5] are the consensus opinion of an expert panel from the European Society for Immunodeficiencies (ESID). These are an important step in improving the outcome for patients with primary immunodeficiency, by initiating suitable screening investigations at an early stage of presentation. Previous guidelines for the diagnosis of primary immunodeficiency have focused upon the assessment of each component part of the immune system (such as phagocytes, or antibodies) [6,7], an approach that is often overly complex for non-immunologists. The textbook approach to immunodeficiency frequently concentrates on recognition of specific organisms (such as predominant viral infections), whereas we now know that there are many other manifestations of primary immunodeficiency, such as recurrent fevers, autoimmunity or predisposition to particular malignancies.

Despite these lofty aims, the ESID protocols are still focused largely on the traditional breakdown of immuno-

Journal compilation © 2006 British Society for Immunology, *Clinical and Experimental Immunology*, **145:** 201–203

deficiency into humoral, cellular and phagocytic defects – but apply a logical screening process that asks the practitioner to first consider the type of clinical presentation as a clue to the type of defect which may be present. A series of basic screening tests are then employed, which permit rapid decision-making regarding the need for further, more elaborate forms of analysis.

There are two key questions that will determine the success or failure of this approach. First, how will general practitioners, general physicians and paediatricians be made aware of these protocols? Effective use of this information will require dissemination far beyond the readership of *Clinical & Experimental Immunology* and the ESID working party will need to work hard to bring this information to the attention of mainstream physicians.

In their current form, there may be some concern that the ESID protocols contain a quantity and depth of information that will be challenging for the busy general practitioner to use. The success of the next step in the project will therefore rely on the clinical readership of this *Journal* and the immunology community at large, in bringing this information to the attention of their medical colleagues. Furthermore, we will need to be prepared to deal with both requests for screening, and having protocols in place for rapid identification and management of patients flagged-up by the screening processes.

Others have made substantial efforts in this direction, with the Jeffrey Modell Foundation in the United States publicizing 'Ten warning signs of primary immunodeficiency' (www.info4pi.org). This information is taught to medical students and medical trainees, and is published in posters and leaflets for clinical teams. In the United Kingdom, the Primary Immunodeficiency Association has also made significant attempts to raise the awareness of non-immunologists (www.pia.org.uk).

The second key question is: are these screening protocols sufficiently sensitive to use in clinical practice? Many primary immunodeficiencies are extraordinarily rare, and it would not be feasible to undertake randomized controlled trials of these processes. The ESID working party is composed of experts who undertake screening for these diseases on a daily basis, and their guidelines should be recognized as a reasonable compromise between expert opinion and evidence-based studies. There will be situations in which a cautious approach to using the protocols is justified, however. For example, the recognition of lymphopenia is an important step in diagnosing primary immunodeficiency in neonates, yet immunologists frequently forget that significantly more children have transient lymphopenia during periods of infection than actually turn out to have a primary immunodeficiency.

The answers to these concerns involve a number of possible solutions. Immunologists must be involved as early as possible in the work-up of patients suspected to have an immunodeficiency. The United Kingdom is fortunate in having a National Health Service (NHS) immunology service which is led largely by clinicians who are dually trained in both clinical and laboratory immunology. There is therefore significant integration of laboratory and clinical practice. In other countries, these services are now divided largely into two camps, making effective communication between the two absolutely essential for effective early diagnosis of these rare disorders. All too often, significantly abnormal laboratory results fail to be communicated to clinicians in an effective and timely manner, presumably because laboratory practitioners feel mistakenly that clinicians will somehow know how to interpret the results. The significant diagnostic delays which are still a feature of these disorders underline the fact that this communication is not currently effective, and that the significance of even basic abnormalities needs to be made clear to clinicians. Involvement of laboratory practitioners is therefore also essential in making these protocols a success. Not only will they need to be able to alert clinicians to significant abnormalities in the screening investigations, but will also need to provide advice about how to proceed through the protocols in a timely and cost-effective manner.

Basic interpretation of laboratory results requires expertise. It remains a significant anomaly that in certain first-world countries, clinicians still have to deliberately request an IgG, an IgM, an IgA level and electrophoresis as separate tests in order to receive a meaningful assessment of serum immunoglobulins, whereas in other countries it is automatically recognized that these individual tests are inseparable and absolutely required for effective interpretation of the results. Many immunological assays are vulnerable to rapid sample degradation, and clinicians will need to be made aware that abnormal results are frequent in patients with sepsis, and that abnormal results should be repeated for confirmation.

The authors of the ESID protocols recognize that this system will need to be revised as experience of using them grows. Geographical factors will need to be taken into consideration, for example, as the baseline incidence of infection rates varies widely around the world, so the threshold of concern for considering immunodeficiency will need to be adjusted to local circumstances. As new immunodeficiencies are identified, the protocols may need to be revised. Ethical considerations are also relevant, as is it fair to identify immunological defects that cannot be treated? This is an issue of particular concern in economically disadvantaged countries. Although it is true that immunological therapies involving biological or genetic therapies or stem cell transplants remain unaffordable for many, this should be considered against the alternative view – that many antibiotics, vaccines, hygiene measures and reproductive advice are cheap, and should be available for all.

Effective use of this information will require close collaboration between all immunologists. In the United Kingdom, extensive regional and national networking within an NHS setting allows for maximum benefit to patients by bringing

together all the relevant clinicians, nurses and scientists in immunology as part of UK–PIN, the Primary Immunodeficiency Network (www.ukpin.org). Other nations such as Canada are also developing an interest in more effective collaboration in clinical networks. Supranational collaboration, for example with the European Society for Immunodeficiencies (ESID) and the Pan-American Group for Immunodeficiency (PAGID) is also important, as is the concept of multinational disease-specific databases and registries. Clearly, there are important benefits to immunological collaboration, and by continuing to exploit this, as well as the ESID protocols and other opportunities for 'outreach' to the non-immunological community, there should be an expectation that the identification and care of immmunodeficient patients in primary and general practice will continue to improve.

References

1 Blore J, Haeney MR. Primary antibody deficiency and diagnostic delay. BMJ 1989; **25**:516–17.

2 Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. Consensus Panel for the Diagnosis and Management of Primary Antibody Deficiencies. BMJ 1994; **308**:581–5.

3 Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol 2005; **58**:546–7.

4 Spickett GP, Askew T, Chapel HM. Management of primary antibody deficiency by consultant immunologists in the United Kingdom: a paradigm for other rare diseases. Qual Health Care 1995; **4**:263–8.

5 de Vries E, Kumararatne DS, Al-Ghonaium A *et al.* Patient-centred screening for primary immunodeficiency. Clin Exp Immunol 2006; **145**:204–14.

6 Folds JD, Schmitz JL. Clinical and laboratory assessment of immunity. J Allergy Clin Immunol 2003; **111**(Suppl. 2):S702–11.

7 Bonilla FA, Bernstein IL, Khan DA *et al.* Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005; **94** (Suppl. 1):S1–63.

