Interfaces in medicine: clinical immunology and allergy

A conference on clinical immunology and allergy, as part of the ‘Interfaces in medicine’ series, was held at the Royal College of Physicians on 5 March, 1993. The meeting tackled common immunological and allergic problems, with special emphasis on practical management.

Allergy

Dr Mansel Haeney (Hope Hospital, Salford) began by recalling that allergy or type I hypersensitivity as a problem dates back to the time of the Egyptian pharaohs in 2640 BC, when Mene became the first recorded victim of a hornet sting. The term ‘allergy’ was coined in 1906 by von Pirquet to refer to ‘changed reactivity’ of the host when meeting an ‘agent’ on a second or subsequent occasion. The current definition of allergy should be restricted to the deleterious consequences that result from reactions against extrinsic allergens.

The diagnosis of allergy depends primarily on a good clinical history. Investigations which may help in establishing a diagnosis of allergy include skin prick testing and measurement of specific IgE antibodies to suspected allergens. A positive skin prick test, together with a careful clinical history, will suffice to make a diagnosis of allergy in many instances. Measuring IgE specific antibodies and total serum IgE is of value only when skin testing is contraindicated, unreliable, or difficult to perform. Limitations of skin prick tests include the occurrence of false positives in asymptomatic individuals and in people with dermatographism, and of false negatives in infancy and the elderly; also the variability of skin reactivity with circadian rhythms, interference by concurrent antihistamine therapy, and poor correlation with genuine food allergy. In these situations measurement of specific IgE antibodies is indicated, as it also is in individuals in whom severe dermatitis precludes skin testing, and in the investigation of suspected venom allergy.

The most widely used technique for measuring specific IgE antibodies is the radioallergosorbent test (RAST). A positive RAST test must be interpreted in the context of the clinical history and does not by itself prove that a particular antigen is responsible for the patient’s symptoms. Both false negative and false positive results may occur, the former due to the presence of IgG antibodies with the same antigenic specificity, and the latter in the presence of extremely high levels of total IgE.

Both RAST testing and skin prick testing are unreliable for the diagnosis of food allergy, underlining once again the importance of taking a good clinical history. ‘Alternative’ allergy tests, such as leucocytotoxicity testing, hair analysis, vega testing, and applied kinesiology, are of dubious value and should be considered to be empirical until shown to be sensitive and specific by randomised controlled studies.

The diagnostic value of total IgE measurement in the investigation of allergic disease has evoked much discussion. Total IgE levels are not necessary in the investigation of allergy and may even be normal in 25% of cases of allergic asthma. In practice, however, for economic reasons some laboratories use total IgE levels as a guide to antigen specific IgE antibody testing.

Food allergy

The thorny issue of food allergy was tackled by Dr Elspeth Young (Amersham). Adverse reactions to food may manifest either as intolerance (non-immunological) or true hypersensitivity reactions (immunologically mediated). True food allergy is serious and may even be fatal. According to a survey carried out in High Wycombe, intolerance to food additives affects between 0.01% and 0.23% of the population in the UK. Similar prevalence figures have been reported from Denmark (0.01%–0.1%). In a subsequent survey in High Wycombe, of intolerance to all kinds of food, prevalence figures of 1.4 to 1.9% were obtained. Interestingly, there was a wide disparity between the number of respondents who thought that they had a problem with intolerance to either additives or to foods, and the final small number in whom it was confirmed by blinded challenge testing.

The diagnostic approach to food allergy begins with taking a careful history and maintaining a dietary diary. Suspected foods are removed from the diet and reintroduced in either a single blind (patient blinded) or double blind manner. The double blind placebo-controlled food challenge, despite its time-consuming nature, remains the gold standard for the diagnosis of food allergy. Skin prick tests and serum levels of food specific IgE antibodies correlate poorly with clinical findings.

Insect venom allergy

Dr Pamela Ewan (Cambridge) discussed the indications and practicalities of desensitisation in patients
with proven insect venom allergy. In patients who have had a systemic reaction (generalised urticaria, laryngeal oedema, bronchospasm, or hypotension) to insect venom the risk of a further generalised reaction ranges from 20% to 60%. Venom immunotherapy reduces this risk to approximately 1%. Immunotherapy itself carries the risk of serious side-effects (anaphylaxis, laryngeal oedema) in a sizable minority of patients. It should therefore be carried out only by appropriately trained physicians in hospital, and should be reserved for patients who have had a severe systemic reaction to the venom (cardiovascular and/or respiratory problems) and in whom venom specific IgE can be demonstrated; the risk of causing adverse side-effects is too great in patients who have only had moderate generalised reactions or only local reactions. Predicting the risk of further reaction in a patient on immunotherapy is difficult. Direct provocation testing with deliberate insect sting challenges in a controlled setting is the most objective method of ascertaining the success of immunotherapy, but in practice it is carried out in relatively few centres. Monitoring venom specific serum IgG and IgE antibody levels has not been of value. The duration of immunotherapy remains contentious, with periods varying from three to five years.

Questions remaining unanswered include the natural history of venom allergy, the immunological factors associated with severe reactions to immunotherapy, and the mechanism of immunotherapy.

Urticaria

Dr J Wilkinson (Amersham) lucidly outlined his views on the investigation and treatment of urticaria. In addition to the standard aetiological classification, it is worth remembering that urticaria may sometimes be the presenting feature of bullous disorders such as pemphigoid and dermatitis herpetiformis.

The investigation of a patient with chronic urticaria requires much thought, and the blunderbuss approach of requesting laboratory tests for an exhaustive list of causes should be avoided. An audit of laboratory tests in 135 patients with urticaria over a five-year period revealed that of 518 tests carried out, only eight were deemed to have been clinically useful. After taking a thorough history, with particular reference to atopy, family history, drugs, foods, periodicity, and coexistent illness, the examination should concentrate on duration of lesions, evidence of bruising or vasculitis, and the presence of other signs. The initial laboratory tests should be limited to a full blood count and erythrocyte sedimentation rate. Other investigations, such as serum IgE levels and complement levels, should only be used if the history and/or examination points towards atopy or urticarial vasculitis. Urticarial vasculitis is characterised by painful rather than itchy wheals lasting over 24 hours. Investigation of thyroid function may occasionally identify a patient with thyrotoxicosis and urticaria.

The majority of cases of acute urticaria respond to a combination of antihistamines and steroids, with adrenaline being reserved for cases accompanied by angioedema. Many patients with chronic urticaria obtain symptomatic relief with antihistamines alone. In a minority of patients with refractory urticaria and angioedema, therapeutic alternatives are combinations of H1 and H2 blockers, ketotifen, danazol (even when C1 inhibitor levels are normal), and low-dose steroids.

Vasculitis

Dr T Wallington (Bristol) described the role of the clinical immunology laboratory in the investigation of suspected vasculitis, concentrating particularly on the use of antineutrophil cytoplasmic antibodies (ANCA) as a diagnostic tool. But the availability of ANCA has not done away with the need to establish a tissue diagnosis in cases of diagnostic difficulty.

Van der Woude's landmark paper in 1985 firmly established the high degree of sensitivity and specificity of the cytoplasmic pattern of ANCA in patients with active Wegener's granulomatosis (WG). The existence of a separate distinct perinuclear ANCA (p-ANCA) pattern was highlighted by Falk and Jennette in 1988 in patients with necrotising, crescentic glomerulonephritis. This was the first of several different p-ANCA patterns to be described. While the c-ANCA staining pattern is produced almost exclusively by antibodies directed against proteinase III, a multiplicity of antigenic targets is responsible for the p-ANCA patterns (myeloperoxidase—MPO, elastase, cathepsin, lactoferrin—LF).

The most widely used technique for detecting ANCA is indirect immunofluorescence (IF), using two sets of neutrophil preparations fixed with ethanol and formaldehyde respectively. While c-ANCA positive sera show the same cytoplasmic staining pattern irrespective of the fixative used, sera producing a p-ANCA pattern on ethanol-fixed neutrophils will revert to showing cytoplasmic staining on formaldehyde-fixed neutrophils. It is unclear why ethanol fixation should cause cytoplasmic antigenic targets (MPO, LF, cathepsin, elastase) responsible for the p-ANCA pattern to migrate to the nucleus.

Difficulties in interpretation of ANCA using the IF technique arise in the presence of antinuclear antibodies (ANA) which can be confused with p-ANCA. For this reason all p-ANCA positive sera must be screened for ANAs on standard rat liver sections or HEp-2 cell preparations. Occasionally anti-nuclear antibodies specifically directed towards granulocyte nuclei (GS-ANA) are seen in patients with Felty's syndrome and ulcerative colitis (Table 1).

Despite these difficulties the IF technique remains, in experienced hands, the gold standard for the detec-
Table 1. Effect of fixative on ANCA pattern using IIF

| Ethanol | Formaldehyde | HEP-2 |
|---------|--------------|-------|
| c-ANCA  | Cytoplasm +  | Cytoplasm + | — |
| p-ANCA  | Nucleus +    | Cytoplasm + | — |
| ANA     | Nucleus +    | Nucleus +  | Nucleus + |
| p-ANCA  | Nucleus +    | Cytoplasm + | Nucleus + |
| + ANA   | Nucleus +    | Cytoplasm - | — |
| GS-ANA  | Nucleus +    | Nucleus +  | — |

GS-ANA: Granulocyte specific antinuclear antibody

tion of ANCA. A variety of solid phase assays to specific antigens have been developed but are as yet poorly standardised, and are unsuitable for routine clinical use.

While most patients (76–94%) with active generalised WG are c-ANCA positive, those with limited disease may be ANCA negative. In general, antibody titres tend to parallel disease activity. In classical polyarteritis nodosa both c-ANCA and p-ANCA patterns may be seen, with p-ANCA predominating in microscopic polyarteritis. p-ANCA positivity may also be seen in up to 10–15% of patients with systemic lupus erythematosus, rheumatoid arthritis, and ulcerative colitis. The rare occurrence of false positive c-ANCA in significant titres in diseases which may mimic WG, eg tuberculosis, non-Hodgkin’s lymphoma, infective endocarditis, serves to emphasise the point that a positive c-ANCA by itself does not equate with a diagnosis of WG.

Treatment of vasculitis

Dr D Adu (Birmingham), presenting the physician’s view of vasculitis, concentrated on the therapeutic aspects and began by posing the question: what is vasculitis? Definitions abound but none is wholly satisfactory, as summed up by the memorable quote: ‘an etymologic quagmire: few who enter the area emerge unscathed’. The treatment of vasculitis is as complicated as its definition and classification. In general, acute treatment consists of high-dose steroids and cyclophosphamide (CP), with the accompanying risk of significant drug-related morbidity in both the short and long term.

In addition to marrow suppression, carcinoma of the bladder is now recognised as a problem in patients treated with long-term cyclophosphamide, particularly in view of the improvement in survival over the past decade. Outstanding questions regarding the use of cyclophosphamide relate to its optimal dose, route of administration, and the frequency of treatment (continuous vs pulse). Interest in pulsed CP has heightened after the demonstration of equal efficacy and less long-term toxicity in comparison with daily oral CP in lupus nephritis. Whether this holds true for patients with WG and related disorders has not been systematically studied.

Alternative treatment options include azathioprine, plasmapheresis, intravenous immunoglobulin (IVig), low-dose methotrexate, and monoclonal antibodies directed against CD4. There is much interest in the role of IVg as an immunomodulator and a double blind placebo controlled trial of IVg in drug-resistant ANCA +ve systemic vasculitis is currently in progress.

Disease activity in vasculitis should be closely monitored using activity scores, serum C-reactive protein levels, and titres of marker antibodies where available (ANCA). Preliminary results on the use of adhesion molecules as a marker of activity suggest that in the absence of renal impairment, serum levels of soluble intercellular adhesion molecule—1 (sCD54) discriminate between patients with active and quiescent disease.

Mr J Dormandy (London) gave the vascular surgeon’s view of vasculitis. Too often in surgical practice the diagnosis is made by exclusion without adequate investigations. The most widely used surgical screening test was still the erythrocyte sedimentation rate.

Vasculitic disorders that may present surgically include leg ulcers in patients with polyarteritis nodosa, Raymond’s phenomenon in SLE, and absent upper-limb pulses in Takayasu’s arteritis. Attempting arterial reconstruction in these cases is fraught with danger and should be avoided.

Immunodeficiency

The session on immunodeficiency was opened by Dr A Cant (Newcastle) with a thought-provoking account of when to suspect immunodeficiency in childhood. It is all too often overlooked as a cause of childhood infection because of the widespread misconception that infections in childhood are the unavoidable result of a maturing immune system. Various scoring systems devised to predict which children with infection should be immunologically investigated have proved inadequate. In one particular study the scoring system failed to pick up nine children with immunodeficiency (two with severe combined immunodeficiency (SCID), one with X-linked agammaglobulinaemia (XLA), and five with cyclical neutropenia). An alternative approach (Table 2) is to consider the possible diagnoses in relation to the age of the child, the infective organism, the organ(s) involved, and other clues in the history and examination.

The question of screening for SCID was raised during discussion. Although a rare disorder with an estimated incidence of one in 66,000 births, the excellent results now obtained with bone-marrow transplantation oblige paediatricians to make the diagnosis early. A potentially cheap screening test currently under investigation would be the age-matched absolute lymphocyte count; persistent lymphopenia would necessitate investigation for SCID.
The management of patients with immunodeficiency was covered by Dr D Webster (Harrow) with particular emphasis on primary antibody deficiency. The mainstay of treatment in antibody deficiency is intravenous immunoglobulin (IVIg) to replace missing antibodies. IVIg preparations currently in use are third generation products prepared from donor pools which specifically exclude hepatitis B surface antigen positive, hepatitis C and HIV antibody positive donors. In patients with poor venous access, subcutaneous immunoglobulin replacement is a feasible alternative. Whenever route is used, it is important to maintain trough serum IgG levels within the normal range to prevent development of or deterioration in pre-existing lung damage. Patients with primary antibody deficiency are prone to develop unusual complications, eg enteroviral meningencephalitis in X-linked agamaglobulinaemia, or ‘sterile’ arthropathy due to mycoplasma, which cause considerable morbidity if not treated early. These disorders tend to be overlooked, particularly in situations where non-immunologists look after the occasional patient(s) with antibody deficiency. Regular immunological follow-up is essential for early diagnosis and appropriate treatment of these conditions.

Bone-marrow transplantation from a suitable donor is the treatment of choice for severe combined immunodeficiency. In cases where a single gene defect has been identified (adenosine deaminase (ADA) deficiency), gene therapy is currently under investigation in the US and the UK. Gene therapy using stem cells transfected with a retroviral vector containing the ADA gene has recently been undertaken for the first time in the UK.

Lifelong antibiotic prophylaxis in patients with complement deficiencies and hyposplenism is of doubtful value and unlikely to meet with patient compliance. What may be more important is proper patient education on the need to start antibiotic treatment at the earliest sign of infection, and immunisation against encapsulated bacteria using Pneumovax, haemophilus conjugate, and meningococcal vaccines.

The treatment of neutrophil defects has received a significant boost with the encouraging results obtained with the use of G-CSF in cyclical neutropenia, and of gamma interferon in the treatment of chronic granulomatous disease.

### Table 2. Infections suggestive of immune deficiency in childhood

| Age       | Infection                      | Immune deficiency                  |
|-----------|--------------------------------|------------------------------------|
| < 6/12    | Persistent candidiasis         | Severe combined immunodeficiency   |
|           | PCP                            |                                    |
|           | Persistent CMV                 | Human immunodeficiency             |
|           | Persistent RSV                 | Immunodeficiency                    |
|           | Persistent enteroviruses       | Virus infection (HIV)              |
|           | PCP                            |                                    |
| 6/12      | Recurrent encapsulated bacterial infection | Antibody deficiency       |
| to 5 yrs  | Aspergillosis                  | Phagocytic—CGD disorder            |
|           | Recurrent abscesses            |                                    |
| > 5 yrs   | Recurrent encapsulated bacterial infection | Antibody—CVI deficiency       |
|           | Meningococcal meningitis       | Terminal complement defect         |
|           |                                |                                    |

| CMV       | Cytomegalovirus,               |
| RSV       | Respiratory syncytical virus   |
| XLA       | X-linked agammaglobulinemia    |
| CGD       | Chronic granulomatous disease  |
| CVI       | Common variable immunodeficiency |
| PCP       | Pneumocystis carinii pneumonia |
preparation to prevent reactions due to anti-IgA antibodies. Once patients are established on a particular IVIg preparation, they should not be switched to another product unless there are compelling clinical reasons for doing so. It is unacceptable to change IVIg preparations for financial reasons alone.

The nursing perspective

Sister Theresa Green (Newcastle) provided the nursing perspective. Home immunoglobulin therapy in the UK was pioneered in Oxford and Harrow in 1986. At present there are 233 patients on the UK home therapy register under the care of ten regional immunology centres. In addition to conducting regular two to three day training courses where the principles of asepsis and venepuncture are emphasised, the home therapy sister plays an important peripatetic role by periodically visiting patients in their homes to iron out any problems.

The general practitioner’s view

The general practitioner’s views on home therapy rounded off the final session. As with other essential but relatively expensive therapeutic agents, such as erythropoietin in chronic renal failure, there has been concern that the imposition of tight drug budgets on general practitioners will make them reluctant to prescribe IVIg. Dr B Mullins (Stillington, Stockton-on-Tees) sought to allay such fears by describing the benefits of IVIg replacement in a 43-year-old patient in his practice who was said to have chronic asthma. In the early 1970s ‘dysgammaglobulinaemia’ had been diagnosed, but the link between this and her recurrent chest infections had been overlooked. Despite regular assessment at the chest clinic, her asthma proved difficult to control, with recurrent infection triggering frequent attacks. Over a period of six months she required nine courses of antibiotics. Not until the patient herself produced an article on hypogammaglobulinaemia from a woman’s magazine was the diagnosis made. Regular IVIg replacement has made a dramatic difference, illustrated by the patient’s symptom diaries.

At the end of this session the chairman invited the views of the audience on who should manage patients with antibody deficiency. Dr E de Sousa (general practitioner, Weybridge), speaking from his hospital experience as a senior house officer who had set up IVIg infusions on antibody-deficient patients, bemoaned the lack of guidance and education on immunodeficiency. He firmly held the view that antibody-deficient patients should be under the direct care of a consultant clinical immunologist. This was echoed by Dr Henrietta Ewart (public health physician, Northampton) who, in her capacity as a purchaser of services, had first-hand experience of the lack of awareness and expertise among non-immunologists in managing

patients with antibody deficiency. It was felt that immunologists in regional centres must visit district general hospitals to heighten awareness of antibody deficiency.

Conclusions

The misconception that clinical immunology is a rarified specialty far removed from patients was successfully laid to rest by the meeting. All the speakers made the point that immunological problems are common and that successful management depends on close cooperation between hospital-based immunologists, other organ based specialists, and the general practitioner in the community.

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