Regular Review

Immunodeficiency and general medicine

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Obvious immunodeficiency diseases are relatively uncommon, but they are of both practical and scientific interest to physicians for several reasons. Firstly, early diagnosis of immunodeficiency permits specific treatment, which provides immediate benefit and also prevents long-term complications. Patients with recurrent infections secondary to hypogammaglobulinaemia stand to gain substantially from recognition of their condition. Secondly, the recognised immunodeficiency disorders may prove to be the most obvious examples of diseases resulting from a variety of deficiencies in host immunity. Finally, the results of research on patients with immunodeficiency diseases are clearly relevant to the pathogenesis of some diseases of unknown aetiology.

Autoimmune diseases, particularly those affecting red cells and granulocytes, are found unusually often in patients with late-onset hypogammaglobulinaemia; elucidating the abnormality in the B lymphocytes that causes the primary disease should provide clues to the nature of similar autoimmune disease encountered in isolation. Similarly, the extraordinarily high incidence and diversity of inflammatory connective-tissue diseases found in patients with deficiency in the complement system suggest that defects in immunity permit the development of unusual host reactions such as dermatomyositis and systemic lupus erythematosus. This review summarises the principal forms of immunodeficiency disease in terms of their clinical features and the underlying defects. A comprehensive textbook designed basically for practising physicians has recently been published.¹

Classification of immunodeficiency disorders—Lymphocytes are derived from bone marrow stem cells whose progeny differentiate along two distinct pathways. T lymphocytes migrate firstly to the thymus; after further differentiation the mature T lymphocytes move to lymphoid organs, where they are responsible for what are classically termed "cell-mediated" immune responses. Nevertheless, the functions of T lymphocytes encompass more than is usually understood by this term. Cytotoxic T lymphocytes recognise and destroy host cells that display foreign antigens. A second population of T lymphocytes improves the efficiency with which antibody-secreting cells (B lymphocytes) produce antibodies to foreign antigens, and are therefore termed "helper" cells. A third population of T lymphocytes, termed "suppressor cells," limits the extent to which the host responds to foreign antigens whether in the form of an antibody or of a cell-mediated immune response. Thesecond category of lymphocytes, B lymphocytes, undergoes a series of recognisable differentiation steps in lymphoid tissues; they are the precursors of the plasma cells that produce specific antibody. The clinical importance of this classification

is strikingly illustrated in the immunodeficiency diseases, since our understanding of these diseases largely depends on the distinction between disorders of the T and B lymphocyte series.

Other factors contribute to host immunity in animal studies, however, though their relative importance varies with different forms of microbial infection. Some immunodeficiency diseases are attributable to corresponding defects in host immunity. Not all the recognised forms of host response have yet been linked with human diseases, but in time the picture will probably be complete. For example, macrophages are important in host defence against several forms of experimental infection, and deficiencies in macrophage function probably underlie human susceptibility to mycobacterial and chronic parasitic infections.

Immunodeficiencies affecting B lymphocytes—One-sixth of patients with hypogammaglobulinaemia have the sex-linked form of the disease.² As in any classical sex-linked disease (such as haemophilia), affected males carry the abnormal gene on their single X chromosome, while carrier females have one normal and one abnormal chromosome. The molecular basis of the defect is unknown, but it probably prevents normal differentiation of B lymphocytes. Serum concentrations of immunoglobulin are low; those of IgA and IgM are virtually undetectable in most cases and low in the remainder.³ Antibody is not produced in response to specific immunisation, and circulating B lymphocytes are undetectable by conventional techniques. Boys with this disorder usually develop symptoms at between 3 months and 2 years of age, since younger infants are protected by maternal antibody. Bacterial infections are common, often in the form of recurrent infections of the respiratory tract such as pneumonia and otitis media. Severe disorders such as septicaemia, osteomyelitis, arthritis, and meningitis occur less commonly. These patients do not have problems with viral infections, except that certain enteroviruses such as echoviruses (which usually produce a self-limiting disorder in normal people) may produce myositis and meningoencephalitis. There are many interesting points of similarity between atypical infection by echoviruses in these children and dermatomyositis in children without any obvious immunodeficiency.

Children with sex-linked hypogammaglobulinaemia also fail to produce antibody to oral polio vaccine, thereby becoming prolonged carriers of this agent; but there is no clear evidence that they are unduly likely to develop paralytic poliomyelitis after natural infection. Some children with this condition develop progressive brain damage in the form of convulsions, mental deterioration, and objective neurological abnorm-

alities⁴⁻⁵—raising the possibility that unidentified viruses may be responsible and so providing a pointer to the aetiology of similar syndromes in children with no obvious defects in antibody production. Children with sex-linked hypogammaglobulinaemia may also develop arthritis, usually attributable to a specific infecting organism.⁶

Though uncommon, sex-linked hypogammaglobulinaemia should be suspected in children with recurrent respiratory infections, and in particular with pneumonia and otherwise increasingly rare diseases such as bronchiectasis and chronic otitis media. While more elaborate investigations are needed to establish the diagnosis beyond doubt, for screening it is sufficient to determine that serum immunoglobulin concentrations are low and that B lymphocytes are undetectable in the peripheral blood. A rare autosomal form of hypogammaglobulinaemia also exists in infancy and may occur in girls,⁷ so that hypogammaglobulinaemia should be considered in infants of either sex when the clinical circumstances are suspicious.

Late-onset hypogammaglobulinaemia is the term used when the disease begins after the age of 2; for convenience it is subdivided into onset in children and onset in adults over the age of 16. The disease is presumed to arise from an acquired defect of maturation of B cells affecting a relatively late stage in the differentiation pathway.⁸⁻⁹ No genetic factors have been convincingly implicated in the pathogenesis of the disorder, but susceptibility may possibly be familial. Alterations in the ratio of IgG subclasses have been described in first-degree relatives¹⁰; the relatives of some patients also have severe hypogammaglobulinaemia¹¹; and an increased incidence of autoantibodies to thyroid and stomach has also been reported in relatives of these patients.¹² There is no evidence of any enzyme deficiency. One theory is that in these patients the B lymphocytes fail to mature because their differentiation is prevented by suppressor T lymphocytes.¹³ Nevertheless, this has not been confirmed in most patients with late-onset hypogammaglobulinaemia,¹⁴ and abnormal suppression probably accounts for hypogammaglobulinaemia in only a few patients with accompanying immunoregulatory disorders.

Most patients with late-onset hypogammaglobulinaemia present with recurrent bacterial infections of the upper or lower respiratory tract. They rarely develop abnormally severe or frequent virus infections.⁵ Pneumonia, pleurisy, and recurrent sinusitis are particularly prominent and, in addition, children commonly suffer from otitis media. Some adults with this disorder develop a granulomatous disease of the lungs resembling sarcoidosis.¹⁵ Others develop chronic polyarthritis with a distribution resembling that of rheumatoid arthritis, and tenosynovitis is a prominent feature; but rheumatoid factor is absent and the synovial membrane is infiltrated with mononuclear cells without plasma cells. No infectious agent has been isolated from the joints of these patients, but typically the arthritis responds promptly to treatment with gammaglobulin, strongly suggesting that infections are responsible.¹⁶ Patients with erosive arthritis and subcutaneous nodules associated with hypogammaglobulinaemia have also been described.¹⁷ Despite the absence of conventional antibodies, Coombs-positive haemolytic anaemia, autoimmune neutropenia, and pernicious anaemia occur with abnormally high frequency in patients with adult-onset hypogammaglobulinaemia.¹ Gastrointestinal symptoms in patients with hypogammaglobulinaemia need careful consideration, for—quite apart from the usual diagnostic possibilities—nodular lymphoid hyperplasia is a common complication and may cause chronic diarrhoea.¹⁸ Diarrhoea is also a prominent

symptom in patients with hypogammaglobulinaemia associated with thymomas.

The treatment of hypogammaglobulinaemia at all ages consists in regular injections of gammaglobulin, prompt treatment of secondary infections after careful microbiological studies, and long-term follow-up.

Selective deficiency of different immunoglobulin classes is also encountered, of which the most common is deficiency of IgA; the incidence in Europe is one person in 700. Most such individuals are symptom free. The extent to which IgA deficiency predisposes to allergic disease and autoimmune diseases is an important and contentious issue needing further studies free from selection bias. Selective deficiency of IgG or IgM is rarer, but some severe bacterial and viral infections have been encountered in the reported cases. Of wider potential interest are the patients with no obvious deficiency in the total concentration of the major immunoglobulin classes who nevertheless fail to make specific antibody in response to certain infections or to antigen challenge.¹⁹ Such observations provoke the suspicion that many atypical or unusually virulent infections in individuals without obvious immunodeficiency may result from the patient's failure to produce specific antibody to the invading micro-organism.

Immunodeficiency affecting T lymphocytes—The most clear-cut example of immunodeficiency affecting the T lymphocytes is the DiGeorge syndrome, resulting from the failure of the thymus and parathyroid glands to develop. The clinical picture is dominated initially by cardiac failure from associated heart lesions and by the features of hypoparathyroidism. These infants are susceptible to viral infections and also to bacterial infections because of their failure to initiate humoral antibody responses. In some infants the failure of thymic development is also associated with immunodeficiency of the B lymphocyte series, producing the condition termed "severe combined immunodeficiency." This disease presents in the first weeks of life with recurrent viral and bacterial infections, chronic diarrhoea, and failure to thrive. Infection by *Pneumocystis carinii* is a common cause of interstitial pneumonia. In some variants of the disease the prognosis is better because the associated hypogammaglobulinaemia is less severe (Nezelof's syndrome).

The combined immunodeficiencies are of scientific interest for two reasons. Firstly, the combined use of thymus and bone-marrow transplants has proved to be the first successful attempt to repair specific immune defects. Secondly, while these disorders were initially attributed to a deficiency of bone-marrow stem cells, specific biochemical defects have been discovered in some cases; one example is absence of adenosine deaminase, which catalyses the conversion of adenosine to inosine.²⁰ The faulty function of both T and B lymphocytes may be attributable to the resulting accumulation of a toxic metabolite; the condition can be corrected by infusing normal red cells containing the missing enzyme.²¹ Deficiency of T lymphocytes in infancy may also be caused by a deficiency of the enzyme purine nucleoside phosphorylase.²² Affected infants may suffer from severe infections with varicella, vaccinia, or cytomegalovirus. The discovery of defects in purine metabolism in children with these rare forms of immunodeficiency is important, because it may provide the clue to subtler abnormalities underlying the pathogenesis of the congenital defects and autoimmune disease that accompany immunodeficiency. Defects in T lymphocytes are also found in the rare inherited neurological disorder ataxia telangiectasia, which results from a defect in DNA repair.²³

Proved T lymphocyte deficiency accounts for few of the

large number of chronic infective and inflammatory diseases of children and adults in which this defect has been postulated. For example, several forms of such deficiency have been invoked in chronic mucocutaneous candidiasis.²⁴ Similarly, defective function in T lymphocytes has been allegedly discovered in patients with connective-tissue disorders such as rheumatoid arthritis and systemic lupus erythematosus. Such reported abnormalities may, however, merely reflect the non-specific effects of disease activity or of vast antigen excess in infectious diseases. Nevertheless, an inherited or acquired inability to handle certain infectious agents may reasonably be postulated in the chronic inflammatory and degenerative disorders of unknown aetiology, and the unequivocal T lymphocyte defects in childhood immunodeficiency disorders provide invaluable models for designing logical studies in more common diseases.

Non-specific host-defence factors—The importance of complement in host defence and the consequences of complement-deficiency states are well recognised.²⁵ Primary defects of neutrophils have been identified in only a few patients with severe recurrent infections. The most important of these disorders are the various forms of primary chronic neutropenia and defects in killing bacteria in diseases such as chronic

granulomatous disease—in which the results of recent biochemical investigations suggest that specific metabolic defects will soon be delineated.²⁶ As with the alleged defects in T lymphocytes, there is still no clear evidence that defects in granulocytes account for the vast mass of chronic inflammatory diseases. While defective function in granulocytes has been described both in vitro and in vivo in a variety of disorders, the primary pathogenic importance of these defects has not been established. The same comments apply to monocyte-macrophage function, which for technical reasons is still difficult to analyse in health and disease.

Conclusions—Immunodeficiency diseases are important causes of chronic and atypical infections. Many of their causes have been well characterised, and their study has stimulated the development of precise techniques for measuring the function of human lymphocytes and granulocytes, for analysing other forms of host defence, and for detecting subtler forms of immunodeficiency in more common disorders.

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