Investigating an immunocompromised child

Anura Weerasinghe[1]

(Key words: immunocompromised child, investigation)

Introduction

The term 'immunocompromised' refers to individuals whose resistance to infection has been reduced by disease (congenital or acquired) or by therapeutic measures such as the treatment of malignant disease or organ transplantation. They present with increased susceptibility to infections. The investigation of such children is directed at finding out which components of the immune system are defective. The type of infection gives a clue to the nature of the abnormality of the immune system and serves as a guide to selection of the appropriate laboratory investigations[1].

Primary immune deficiency is rare[2]. IgA deficiency, which is found in 1:600 in the United States, is the commonest primary immunodeficiency[3]. Data from our studies suggest that IgA deficiency is the commonest humoral deficiency in Sri Lanka as well[4,5].

Acquired immunodeficiencies are much more common but are often less precisely defined in terms of immunological mechanisms[6]. They can in many cases be best understood against the background of the more specific defects[7,8]. They also include iatrogenic causes and immunosuppression. Malnutrition, deliberate immunosuppression, unwanted complications of certain therapies and immunosuppression due to tumours of the immune system and HIV infection constitute this group.

Investigations of an immunocompromised child are directed at detecting defects of humoral, phagocytic and cellular components of the immune system. Furthermore, defects in certain enzymes can be detected by novel molecular biological techniques.

Evaluation of antibody deficiency disorders[9,10]

Zonal electrophoresis of serum

This initial screening investigation, which is widely available, enables a tentative diagnosis to be made rapidly. Antibody deficiency is suspected by the presence of hypogammaglobulinaemia on an electrophoretic strip. However, a normal electrophoretic

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pattern does not exclude significant antibody deficiency. Hence quantification of immunoglobulin concentration is essential.

Measurement of serum immunoglobulins

The first stage is to measure concentrations of IgG, IgA and IgM in serum. Radial immunodiffusion is a relatively economical method. Immunoglobulin deficiency is diagnosed if levels are below the 95% confidence limits of age matched control populations. If antibody deficiency is suspected on clinical grounds and yet IgG, IgA and IgM levels are normal, IgG subclasses should be measured and the functional antibody status assessed. Reduced or absent antibody responses to specific antigens can rarely be seen with normal or raised serum immunoglobulin concentrations.

Interpretation of results of serum immunoglobulin estimation

The age of the child is important in making a diagnosis of immunodeficiency. Almost all infants go through a period of hypogammaglobulinaemia at approximately 5-6 months of age. At this time, many normal infants begin transiently to experience recurrent respiratory tract infections. This phenomenon is physiological and is known as hypogammaglobulinaemia of infancy. The presence of normal serum levels of IgM or IgA argues strongly against a diagnosis of X-linked hypogammaglobulinaemia. However, some infants with transient hypogammaglobulinaemia may also fail to produce normal amount of IgM or IgA.

Further evaluation of a hypogammaglobulinaemic child

Assessment of isohaemagglutinins

Isohaemagglutinins that result from natural immunization are normally present in infants of the appropriate blood group by 1 year of age. Titres of anti-A and anti-B should be greater than 1:4 in normal individuals.

Assessment of functional antibody status by measuring antibody concentrations against a panel of specific antigens

The presence of antibodies against certain vaccines suggests ability to respond to these vaccines. However, live vaccines should not be used in children with suspected immunodeficiency. This form of assessment is of value in distinguishing X-linked hypogammaglobulinaemia from transient hypogammaglobulinaemia of infancy and in detecting antibody deficiency in the presence of normal or increased immunoglobulin levels.

Another situation, in which immunodeficiency occurs in the presence of certain immunoglobulins is hyper-IgM syndrome. This syndrome, which is characterized by an increased level of IgM associated with a deficiency of IgG and IgA, is relatively rare and in most instances appears to be inherited in a X-linked manner.

Assessment of blood surface markers of lymphocytes

The number of B cells and T cells can clearly be assessed by flowcytometry. The different surface markers of lymphocytes include CD3 in T cells, CD19 & CD20 in B cells and CD16, CD56 & CD57 in NK cells. T lymphocytes of peripheral blood can be subdivided into two major groups namely CD4 and CD8. The lack of CD4 cells as seen in acquired immunodeficiency syndrome (AIDS) results in a severe immunodeficiency state. Isolated B cell deficiency occurs in Bruton X-linked agammaglobulinaemia and both B & T cells are involved with severe combined immunodeficiency (SCID) in which the defect is at the level of stem cells. Enzyme deficiencies can result in SCID. Deficiency of adenosine deaminase and purine nucleoside phosphorylase constitutes the important enzymes in this group.

Clinical syndromes

Immunodeficiency is sometimes associated with certain clinical features resulting in well-known clinical entities. Di George syndrome is immunodeficiency associated with hypoparathyroidism and congenital aplasia or hypoplasia of the thymus. Wiskott-Aldrich syndrome consists of eczema, recurrent pyogenic infection, and thrombocytopenia associated with decreased IgM levels. Similarly, selective IgA deficiency resulting in recurrent sino-pulmonary infection may be associated with ataxia-telangiectasia.

Neutrophil function tests[11]

Tests of neutrophil funciton are used in the assessment of suspected immunodeficiency. The types of clinical presentation are often characteristic and the history suggests the need for assessment of neutrophil function.

Patients tend to get recurrent staphylococcal infections especially skin infections, and have chronic gingivitis. Neutropenia itself is the most common neutrophil abnormality resulting in immunodeficiency and primary defects of neutrophil funciton are rare. There is no point in requesting neutrophil function tests if the circulating neutrophil count is less that 1×10^9/L. Secondary defects of neutrophil function are the commonest type of abnormality seen in practice. In such cases neutrophil function should only be assessed when the disease concerned is well-controlled. This is particularly so in the acute phase of a severe infection, when secondary depression of neutrophil function may be present and lead one to suspect a functional neutrophil abnormality as the cause of the infection. Neutrophil function tests done after the resolution of an infection are most likely to be clinically helpful.

Killing by neutrophils can be broken down into several phases listed here in physiological order

1. Mobilization from marrow stores.

2. Movement towards a site of inflammation (chemotaxis).

3. Interaction of opsonized particles with receptors on neutrophil surfaces.

4. Ingestion of particles (phagocytosis).

5. Development of respiratory burst.

6. Killing and digestion of micro-organisms.

By far the commonest neutrophil function test carried out is the nitrobluetetrazolium (NBT) reduction test, a technique for screening neutrophil respiratory burst. Ingestion of organisms by neutrophils is followed by degranulation; the lysosomal granules fuse with the phagocytic vacuoles into which they empty their contents. The killing potential of neutrophils is dependent on the release of enzymes, but this is usually not sufficient for optimal killing. The most efficient bactericidal activity occurs during the 'respiratory burst' in which products of molecular oxygen and other toxic reactants are produced. The NBT test measures this oxidative burst by incubation of neutrophils with a suitable stimulus, phorbol myristate acetate and the soluble yellow dye NBT Following the production of superoxide radicals, NBT is reduced to an insoluble blue formazan which is deposited in the granules. Neutrophils from patients with chronic granulomatous disease (CGD) do not exhibit dye reduction.

Evaluating the complement system[12,13]

As complement plays a major role in the elimination of bacteria and immune complexes, it is not surprising that

inherited complement deficiencies are associated with increased risk of developing severe recurrent bacterial infections and immune complex diseases. Deficiencies of complement C3 are associated with recurrent bacterial infection similar to those with agammaglobulinaemia. Defects in the terminal components (C6-9) are associated with an increased susceptibility to recurrent neisserial infection.

Immunochemical and functional assays can be used for measuring individual components of the complement cascade. The immunochemical methods include radial immunodiffusion (RID), nephelometry and enzyme linked immunoadsorbent assay (ELISA). Low levels of complement components may indicate either complement consumption or deficiency. Functional assays such as total haemolytic complement (CH50) assay and alternative pathway haemolytic complement (AP-CH50) assay are used to detect complement component deficiencies.

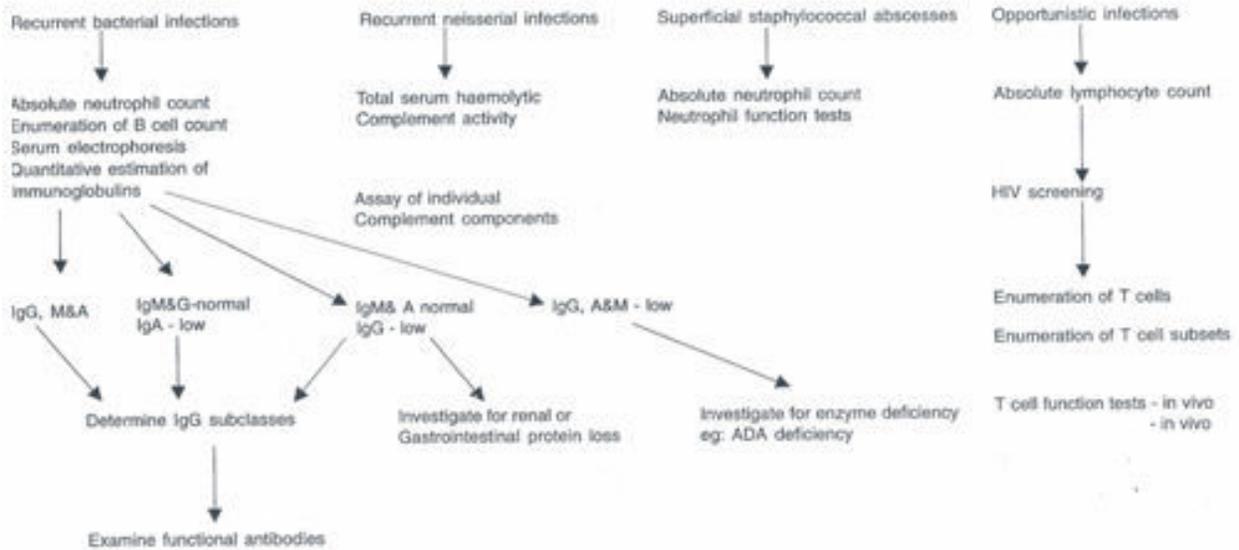**Evaluating T cell defects**[14,15,16]

A clinical history of opportunistic infections warrant investigating for T cell defects. The simplest screening test is the absolute lymphocyte count. As 70% of peripheral lymphocytes are T cells, T lymphocytopenia will be reflected in the absolute lymphocyte count. Even in the absence of apparent lymphocytopenia, if the clinical picture suggests an immunodeficiency, further tests are indicated. Screening for HIV infection should be carried out early in the evaluation. Flowcytometric assessment of lymphocytes can detect quantitative defects in lymphocyte subsets (CD4 and CD8). Qualitative defects of T cells are detected in vivo with the tuberculin skin test (Mantoux test). Functional assays in vitro are based on the proliferation of T cells in response to signals provided by mitogens such as concanavalin A.

Genetic defects constitute an important cause of immunodeficiency. Therefore, evaluation of an immunocompromised child is not complete unless adequate family studies are carried out.

References

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Flow chart for investigation of immunodeficiency
Which infections are present ?

Recurrent bacterial infections

↓

Absolute neutrophil count
Enumeration of B cell count
Serum electrophoresis
Quantitative estimation of
immunoglobulins

↓

IgG, M&A

IgM&G-normal
IgA - low

IgM& A normal
IgG - low

IgG, A&M - low

Determine IgG subclasses

↓

Examine functional antibodies

Investigate for renal or
Gastrointestinal protein loss

Investigate for enzyme deficiency
eg: ADA deficiency

Recurrent neisserial infections

↓

Total serum haemolytic
Complement activity

Assay of individual
Complement components

Superficial staphylococcal abscesses

↓

Absolute neutrophil count
Neutrophil function tests

Opportunistic infections

↓

Absolute lymphocyte count

↓

HIV screening

↓

Enumeration of T cells

Enumeration of T cell subsets

T cell function tests - in vivo
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Enumeration of T cells

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T cell function tests - in vivo
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