

Clinical Focus on Primary Immune Deficiencies

ISSUES AND INFORMATION ON CURRENT TOPICS

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The Clinical Presentation of Primary Immunodeficiency Diseases

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The primary immunodeficiency diseases were originally viewed as rare disorders, characterized by severe clinical expression early in life. However, it has become clear that these diseases are not as uncommon as originally suspected, that their clinical expression can sometimes be relatively mild, and that they are seen nearly as often in adolescents and adults as they are in infants and children (Table 1). In fact, immunodeficiency may present so subtly that the diagnosis will be made only if

Table 1:
Primary Immunodeficiency

- Is Not Rare
- May Present at Any Age
- Does Not Always Present with Severe Infections

the physician is alert to that possibility.

Early diagnosis of immunodeficiency is important so that appropriate therapy can be instituted before there has been end-organ damage. Furthermore, because some primary immunodeficiency diseases are inheritable, early diagnosis is essential for making genetic information available to the families of affected individuals.

Table 2:
Clinical Features of Immunodeficiency

- Increased susceptibility to infection
 - Chronic/recurrent infections without other explanation
 - Infection with organism of low virulence
 - Infection of unusual severity
- Autoimmune or inflammatory disease
- Syndrome complex

This article will review the most common clinical signs and symptoms of primary immunodeficiency diseases, and discuss the most useful screening laboratory tests.

Clinical Manifestations

Patients with primary immunodeficiency diseases most often are recognized because of their increased susceptibility to infection, but these patients may also present with a variety of other clinical manifestations (Table 2). In fact, non-infectious manifestations, such as autoimmune disease, may be the first or the predominant clinical symptoms of the underlying immunodeficiency. Other immunodeficiency diseases may be diagnosed because of their known association with syndrome complexes.



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Immune Deficiency Foundation, the national nonprofit organization devoted to research and education for the primary immune deficiency diseases, publishes other materials for physicians and healthcare professionals (eg. Physician's Primer and Guide for Nurses) and for patients (eg. Patient and Family Handbook, Our Immune System, and Newsletter). For Information about our programs, patient groups and publications, call 1-800-296-4433.

Infectious Manifestations

An increased susceptibility to infection is the hallmark of the primary immunodeficiency diseases. In most patients, the striking clinical feature is the chronic or recurring nature of the

a patient who presents with infection caused by *Pneumocystis carinii* or another opportunistic pathogen is likely to be immunodeficient even if it is his/her first recognized infection.

The type of pathogen and the location of the infection may give valuable insight into the nature of the immunologic defect. Individuals with defects in cell-mediated immunity characteristically have difficulty with viruses and fungi. Individuals with antibody deficiencies are unusually susceptible to encapsulated bacteria and enteroviruses. Patients with complement deficiencies most often present with bacteremia, septic arthritis and meningitis, caused by encapsulated bacteria. And finally, phagocytic disorders are characterized by infections of the skin and reticuloendothelial system (lymph nodes, spleen and liver).

autoimmune thyroiditis), or may involve a number of different target organs (e.g., vasculitis, systemic lupus erythematosus, rheumatoid arthritis). The autoimmune and inflammatory diseases are more commonly seen in particular primary immunodeficiency diseases, most notably common variable immunodeficiency, selective IgA deficiency, chronic mucocutaneous candidiasis, and deficiencies of early components of the classical complement pathway (C1-C4).

Occasionally a disorder that appears to be autoimmune in nature may, in fact, be due to an infectious agent. For example, the dermatomyositis that is sometimes seen in patients with X-linked agammaglobulinemia is really a manifestation of chronic enterovirus infection and not autoimmune disease.

Table 3:

Autoimmune or Inflammatory Manifestations of Primary Immunodeficiency

Target Cells

- Hemolytic anemia
- Immune thrombocytopenia
- Thyroiditis

Target Tissues

- Vasculitis
- Systemic lupus erythematosus
- Rheumatoid arthritis

Associated Diseases

- Common variable immunodeficiency
- Selective IgA deficiency
- Chronic mucocutaneous candidiasis
- Complement pathway deficiencies

infections rather than the fact that individual infections are unusually severe. It is difficult to assign a precise frequency of infections that defines increased susceptibility. As a guideline, immunodeficiency should be suspected when a patient has more than one pneumonia per decade, chronic sinusitis, chronic bronchitis without a history of smoking, increasing numbers of ear infections after early childhood, chronic diarrhea or recurrent bacteremia. In some instances the patient not only has recurrent infections, but one or more of these is either unusually severe (e.g., sepsis), leads to an unexpected complication (e.g., empyema or fistula formation), or is caused by an organism of relatively low virulence (e.g., aspergillus).

Not all immunodeficient patients are diagnosed after recurrent infections. In some, the first infection may be unusual enough to raise the question of immunodeficiency. For example,

Autoimmune and Inflammatory Manifestations

Immunodeficient patients can present with autoimmune or chronic inflammatory diseases. It is thought that the basic abnormality leading to immunodeficiency may also lead to faulty discrimination between self and non-self, and thus to autoimmune disease. The manifestations of these disorders (Table 3) may be limited to a single target cell or organ (e.g., autoimmune hemolytic anemia or thrombocytopenia,

Immunodeficiency Syndromes

Immunodeficiency can also be seen as one part of a constellation of signs and symptoms in a syndrome complex. In fact, the recognition that a patient has a syndrome in which immunodeficiency occurs may allow a diagnosis of immunodeficiency to be made before there are any clinical manifestations of that deficiency (Table 4). Children with the DiGeorge Syndrome are usually identified initially because of the neonatal presentation of congenital heart dis-

Table 4:
Examples of Immunodeficiency Syndromes

<u>Syndrome</u>	<u>Clinical Presentation</u>	<u>Immunologic Abnormality</u>
DiGeorge syndrome	Congenital heart disease Hypoparathyroidism Abnormal facies	Thymic hypoplasia
Wiskott-Aldrich syndrome	Thrombocytopenia Eczema	Variable B- and T-lymphocyte dysfunction
Ataxia-Telangiectasia	Ataxia Telangiectasia	Variable B- and T-lymphocyte dysfunction
Ivemark syndrome	Congenital heart disease Bilateral 3-lobed lungs	Asplenia
Polyendocrinopathy syndrome	Endocrine organ dysfunction	Chronic mucocutaneous candidiasis

ease and/or hypocalcemic tetany. This should lead to T-lymphocyte evaluation prior to the onset of opportunistic infections. Similarly, a diagnosis of Wiscott-Aldrich Syndrome can often be made in young boys with eczema and thrombocytopenia even prior to the onset of infections.

LABORATORY EVALUATION

Although immune system dysfunction can be suspected by the clinician after careful review of the history and physical exam, specific diagnoses are rarely evident without the use of the laboratory. However, the types of infections and other symptoms should help to focus the laboratory workup on specific parts of the immune system (Table 5). Patients with antibody deficiency typically have sinopulmonary infections as a prominent presenting feature. Deficiency of cell-mediated immunity predisposes individuals to develop infections caused by *Pneumocystis carinii*, other fungi and a variety of viruses. Abnormalities of complement most often lead to bacterial sepsis or immune

complex-mediated diseases, whereas phagocytic dysfunction should be suspected when patients have recurrent skin infections or visceral abscesses.

Screening tests that should be performed in almost all patients include a complete blood count (CBC) with differential and quantitative measurement of serum immunoglobulins. Other tests should be guided by the clinical features of the patient (Table 6). Finally, whenever primary immunodeficiency is suspected, consideration must also be given to secondary causes of immunodeficiency including HIV infection, therapy with anti-inflammatory medications (e.g., corticosteroids), and other underlying illnesses (e.g., lymphoreticular neoplasms).

Examination of the Peripheral Blood Smear

The CBC with examination of the blood smear is an inexpensive and readily available test that provides important diagnostic information relating to a number of immunodeficiency diseases (Table 6). Neutropenia most often occurs secondary to immunosuppressive drugs,

infection, malnutrition and autoimmunity, but may be a primary problem (congenital or cyclic neutropenia). Persistent neutrophilia is characteristic of leukocyte adhesion molecule deficiency, and abnormal cytoplasmic granules may be seen in the peripheral blood smear of patients with Chediak-Higaski Syndrome.

The blood is predominately a "T cell organ", i.e., the majority (50-70%) of peripheral blood lymphocytes are T cells whereas only 5-15% are B cells. Therefore, lymphopenia is often a presenting feature of T cell or combined immunodeficiency disorders such as severe combined immunodeficiency disease and DiGeorge Syndrome.

Thrombocytopenia may occur as a secondary manifestation of immunodeficiency, but is often a presenting manifestation of the Wiskott-Aldrich Syndrome. A unique finding in the latter group of patients is an abnormally small platelet volume, a measurement that is easily made by automated blood counters.

Examination of red blood cell morphology can yield clues about splenic function. Howell-Jolly bodies may be visible in peripheral blood

Table 5:
Patterns of Illness Associated with Primary Immunodeficiency

<u>Disorder</u>	<u>Illnesses</u>	
Antibody	<u>Infection</u> Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	<u>Other</u> Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, <i>Pneumocystis carinii</i> , viruses) Gastrointestinal (viruses) Skin, mucous membranes (fungi)	
Complement	Sepsis and other blood-borne (streptococci, pneumococci, neisseria)	Autoimmune disease (Systemic lupus erythematosus, glomerulonephritis)
Phagocytosis	Skin, reticuloendothelial system, abscesses (staphylococci, enteric bacteria, fungi, mycobacteria)	

in cases of splenic dysfunction or asplenia. However, the converse is not always true and absence of Howell-Jolly bodies does not guarantee that splenic function is normal.

Evaluation of Humoral Immunity

Measurement of serum immunoglobulin levels is an important screening test to detect immunodeficiency for three reasons: (1) More than 80% of patients with primary disorders of immunity will have abnormalities of serum immunoglobulins; (2) Immunoglobulin measurements yield indirect information about several disparate aspects of the immune system because immunoglobulin synthesis requires the coordinated function of B lymphocytes, T lymphocytes and monocytes; and (3) The measurement of serum immunoglobulin levels is readily available, highly reliable and relatively inexpensive.

The initial screening test for humoral immune function is the quantitative measurement of serum immunoglobulins. Neither serum protein electrophoresis nor immunoelectrophoresis is sufficiently sensitive or quantitative to be useful for this purpose. Quantitative measurements of serum IgG, IgA and IgM will

identify patients with panhypogammaglobulinemia as well as those with deficiencies of an individual class of immunoglobulins, such as a selective IgA deficiency. Interpretation of results must be made in view of the marked variations in normal immunoglobulin levels with age. Therefore, age-related normal values must always be used for comparison.

A clue to immunodeficiency may be a low normal IgG level in an individual with recurrent infections. In such cases, it is critical to assess antibody function in addition to immunoglobulin level. Antibody levels generated in response to childhood immunization with tetanus toxoid or the Hemophilus influenzae protein conjugate vaccines are usually the most convenient to measure. In children over the age of 18-24 months, it is also important to assess antibody responses to polysaccharide antigens because these responses may be deficient in some patients who respond normally to protein antigens. Antibody can be measured after immunization with pneumococcal capsular polysaccharide vaccine. (The pneumococcal polysaccharide/protein conjugate vaccines are not useful for this purpose.) Alternatively, since the ABO blood group antigens are polysaccha-

rides, anti-polysaccharide antibody can be assessed by quantitating isoagglutinin titers. In either case, anti-polysaccharide antibody measurements are generally useful only in children above the age of 2 years, since normal children of younger age may not have significant responses.

The role for IgG subclass measurements is controversial. There are four subclasses of IgG, and selective deficiencies of each of these have been described. However, the significance of an IgG subclass deficiency in the presence of normal antibody responses to protein and polysaccharide antigens is not known. Many physicians, therefore, rely upon antibody measurements and find that information about IgG subclass levels adds to expense but not to diagnosis.

Evaluation of Cell-Mediated Immunity

Testing for defects of cell-mediated immunity is relatively difficult because of the lack of good screening tests. Lymphopenia is suggestive of T-lymphocyte deficiency because T lymphocytes comprise the majority (50-70%) of peripheral blood mononuclear cells. However, lymphopenia is not always present in patients with T lymphocyte functional defects. Similarly, the lack of a thymus silhouette on chest x-ray is rarely helpful in the evaluation of T lymphocyte disorders because the thymus of normal children may involute following stress and give the appearance of thymic hypoplasia.

Indirect information about T cell function may be obtained by enumerating peripheral blood T lymphocytes with appropriate monoclonal antibodies (anti-CD2 or CD3 for total T cells, anti-CD4 for T-helper cells, anti-CD8 for T-cytotoxic cells). Patients with severe combined immunodeficiency and DiGeorge Syndrome generally have decreased numbers of both CD4 and CD8 T lymphocytes. In contrast, patients infected with HIV typically have a selective deficiency of CD4 lymphocytes. All patients with reduced T lymphocyte function or reduced CD4 lymphocyte number should be tested for HIV infection.

Delayed type hypersensitivity (DTH) skin

Table 6:
Screening Tests for Primary Immunodeficiency

<i><u>Suspected Abnormality</u></i>	<i><u>Diagnostic Tests</u></i>
Antibody	Quantitative immunoglobulins (IgG, IgA, IgM) Antibody response to immunization
Cell-mediated immunity	Lymphocyte count T lymphocyte enumeration (CD4, CD8) HIV serology Delayed type hypersensitivity skin tests
Complement	Total hemolytic complement (CH ₅₀)
Phagocytosis	Neutrophil count Nitroblue tetrazolium (NBT) dye test

testing with a panel of antigens is another screening method for older children and adults. A standardized panel of antigens prepared for DTH testing should be used. The presence of one or more positive delayed-type skin tests is generally indicative of intact cell-mediated immunity. However, there are significant limitations to this testing: (1) Prior exposure to antigen is a prerequisite; (2) Normal patients may have transient depression of DTH with acute viral infections such as infectious mononucleosis; (3) A positive skin test to some antigens does not insure that the patient has normal cell-mediated immunity to all antigens (e.g., patients with chronic mucocutaneous candidiasis have a limited defect in which cell-mediated immunity is generally intact except for their response to candida); and (4) Normal children under the age of 12 months frequently are unresponsive to all of the antigens in the panel. DTH skin tests are, therefore, generally not helpful for evaluation of suspected T-lympho-

cyte abnormalities that present early in life (e.g., severe combined immunodeficiency or DiGeorge Syndrome).

Evaluation of the Complement System

Most of the genetically determined deficiencies of complement can be detected with the total serum hemolytic complement (CH_{50}) assay. Since this assay depends on the functional integrity of the classical complement pathway (C1 through C9), a severe deficiency of any of these components leads to a marked reduction or absence of total hemolytic complement activity. Alternative pathway deficiencies (e.g., factor H, factor I and properdin) are extremely rare; they may be suspected if the CH_{50} is in the low range of normal and the serum C3 level is low. The final identification of the specific complement component that is deficient usually rests on both functional and immunochemical tests, and highly specific assays have been developed for each of the individual components.

Evaluation of Phagocytic Cells

Evaluation of phagocytic cells usually entails assessment of both their number and their function. Disorders, such as congenital agranulocytosis or cyclic neutropenia, that are characterized by a deficiency in phagocytic cell number, can be easily detected by using a white blood cell count and differential. Beyond that, assessment of phagocytic cell function is relatively specialized because it depends upon a variety of in vitro assays including measurement of directed cell motility (chemotaxis), ingestion (phagocytosis) and intracellular killing (bactericidal activity). The most common of the phagocyte function disorders, chronic granulomatous disease, can be identified by the nitroblue tetrazolium (NBT) dye test, that measures the oxidative metabolic response of neutrophils and monocytes.

REFERRAL TO A SPECIALIST:

Patients should be sent for confirmatory or more specialized tests if screening tests are abnormal, or even if all screening tests are normal but the clinical features are highly suggestive of immune system dysfunction.

SUGGESTED READING

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