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The Immune Systems

Evaluation of Suspected Immunodeficiency

Recurrent infections or fevers in children are among the most frequent clinical dilemmas for primary care physicians.The number of children suspected of having primary or secondary immunodeficiency far exceeds the number of actual cases, as most patients with recurrent infections do not have an identifiable immunodeficiency disorder .A major reason for the apparent high rate of recurrent infections among children is repeated exposure to infectious agents in child care and other group settings.

Primary care physicians must have a high index of suspicion if defects of the immune system are to be diagnosed early enough that appropriate treatment can be instituted before irreversible damage develops.

Evaluation of immune function should be initiated for children with clinical manifestations of a specific immune disorder or with unusual, chronic, or recurrent infections such as

- (1) One or more systemic bacterial infections (sepsis, meningitis).
- (2) Two or more serious respiratory or documented bacterial infections (cellulitis, draining otitis media, pneumonia, lymphadenitis) within 1 yr.
- (3) Serious infections occurring at unusual sites (liver, brain abscess).
- (4) Infections with unusual pathogens *(Aspergillus, Serratia marcescens, Nocardia, Burkholderia cepacia).*
- (5) Infections with common childhood pathogens but of unusual severity.
- Additional clues to immunodeficiency include: >8 ear infections per yr; >2 serious sinus infections per yr; >2 mo treatment with antibiotics with poor results; failure to thrive with or without chronic diarrhea; and the need for intravenous antibiotics to successfully treat an infection usually treated with oral antibiotics.

The initial evaluation of immunocompetence includes a thorough history, physical examination, and family history.

Initial Immunologic Testing of the Child with Recurrent Infections

COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE
Absolute lymphocyte count (normal result rules against T-cell defect) Absolute neutrophil count (normal result rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections) Platelet count (normal result excludes Wiskott-Aldrich syndrome) Howell-Jolly bodies (absence rules against asplenia) Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)
SCREENING TESTS FOR B-CELL DEFECTS
IgA measurement; if abnormal, IgG and IgM measurement Isohemagglutinins Antibody titers to tetanus, diphtheria, *Haemophilus influenzae,* and pneumococcus
SCREENING TESTS FOR T-CELL DEFECTS
Absolute lymphocyte count (normal result indicates T-cell defect unlikely) *Candida albicans* intradermal skin test: 0.1 mL of a 1 : 1,000 dilution for patients ≥6 yr, 0.1 mL of a 1 : 100 dilution for patients <6 yr
SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS
Absolute neutrophil count Respiratory burst assay
SCREENING TEST FOR COMPLEMENT DEFICIENCY
CH_{50}

- **Primary Defects of Antibody Production**

Of all of the primary immunodeficiency diseases, those affecting antibody production are most frequent. Selective absence of serum and secretory IgA is the most common defect, with rates ranging from 1/333 to 1/18,000 persons among different races. By contrast, agammaglobulinemia occurs with a frequency of only 1/10,000 to 1/50,000 persons. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria or a history of failure of responding to antibiotic treatment; some individuals with selective IgA deficiency or infants with transient hypogammaglobulinemia may have few or no infections.

X-LINKED AGAMMAGLOBULINEMIA (XLA)

Patients with X-linked agammaglobulinemia (XLA), or **Bruton agammaglobulinemia,** have a profound defect in B-lymphocyte development resulting in severe hypogammaglobulinemia, an absence of circulating B cells, small to absent tonsils, and no palpable lymph nodes.

CLINICAL MANIFESTATIONS.

Most boys afflicted with XLA remain well during the 1st 6–9 mo of life by virtue of maternally transmitted IgG antibodies. Thereafter, they acquire infections with extracellular pyogenic organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* unless they are given prophylactic antibiotics or immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis. Infections with *Mycoplasma* are also particularly problematic. Chronic fungal infections are seen; *Pneumocystis carinii* pneumonia rarely occurs. Viral infections are usually handled normally with the exceptions of hepatitis viruses and enteroviruses. Several examples of paralysis after live polio vaccine administration have occurred, and chronic, eventually fatal central nervous system infections with various echoviruses have also occurred. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against enteroviruses. Viral-associated myositis resembling dermatomyositis has been observed. Growth hormone deficiency has also been reported in association with XLA.

DIAGNOSIS.

The diagnosis of XLA should be suspected if **lymphoid hypoplasia,** with minimal or no tonsillar tissue and no palpable lymph nodes, is found on physical examination, and serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits for appropriate age- and race-matched controls, usually with total immunoglobulin <100 mg/dL. Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in this disorder, whereas they are normal in transient hypogammaglobulinemia of infancy.

Flow cytometry is an important test to demonstrate the absence of circulating B cells, which will distinguish this disorder from common variable immunodeficiency and from transient hypogammaglobulinemia of infancy

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells. It has also been called "**acquired hypogammaglobulinemia**" because of a generally later age of onset of infections. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that echovirus meningoencephalitis is rare in patients with CVID. In contrast to XLA, the sex distribution in CVID is almost equal, the age of onset is later (although it may be present in infancy), and infections are less severe

Treatment of B-Cell Defects

Except for the CD40 ligand defect and XLP, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of intravenous immunoglobulins are the only effective treatments for primary B-cell disorders.

. **IVIG (400 mg/kg/mo)** achieves trough IgG levels close to the normal range.

Primary Defects of Cellular Immunity In general, patients with defects in T-cell function have infections or other clinical problems that are more severe than in patients with antibody deficiency disorders these individuals rarely survive beyond infancy or childhood. Transplantation of thymic tissue, or of major histocompatibility complex (MHC)–compatible sibling or haploidentical (half-matched) parental hematopoietic stem cell, is the treatment of choice for patients with primary T-cell defects.

THYMIC HYPOPLASIA (DiGeorge SYNDROME)

Thymic hypoplasia results from dysmorphogenesis of the 3rd and 4th pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal, atrial, and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears .The diagnosis is often first suggested by hypocalcemic seizures during the neonatal period.

DiGeorge syndrome occurs in both males and females. Microdeletions of specific DNA sequences from chromosome 22q11.2,

- Variable hypoplasia of the thymus and parathyroid glands defines **partial DiGeorge syndrome,** which is more frequent than total aplasia;
- Aplasia is present in <1% of patients with DiGeorge syndrome and defines **complete DiGeorge syndrome**. Approximately one third of infants with complete DiGeorge syndrome have **CHARGE association**. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Concentrations of serum immunoglobulins are usually normal, but IgA may be diminished and IgE elevated. Other laboratory findings vary depending on the degree of thymic dysfunction.

Absolute lymphocyte counts are usually only moderately low for age. The CD3 T-cell counts are variably decreased in number, corresponding to the degree of thymic hypoplasia, resulting in an increased percentage of B cells. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Thymic tissue, when found, contains Hassall corpuscles, normal density of thymocytes, and corticomedullary distinction. Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.

Treatment.

The immune deficiency in the complete DiGeorge syndrome is correctable primarily by cultured unrelated thymic tissue transplants or non-irradiated unfractionated bone marrow or peripheral blood transplantation from an HLA-identical sibling.

Primary Combined Antibody and Cellular Immunodeficiencies

Patients with combined antibody and cellular defects have severe, frequently opportunistic infections that lead to death in infancy or childhood unless they are provided hematopoietic stem cell transplantation early in life. These are thought to be rare defects, although the true incidence is unknown because there is no newborn screening for any of these defects. It is possible that many affected children die of infection during infancy without being diagnosed.

Severe Combined Immunodeficiency (SCID)

The syndromes of SCID are caused by diverse genetic mutations that lead to absence of all adaptive immune function and, in some, a lack of natural killer (NK) cells. Patients with this group of disorders have the most severe immunodeficiency

CLINICAL MANIFESTATIONS.

Affected infants present within the 1st few months of life with recurrent or persistent diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections. Growth may appear normal initially, but extreme wasting usually ensues after diarrhea and infections begin. Persistent infections with opportunistic organisms including *Candida albicans, Pneumocystis carinii (jiroveci),* varicella-zoster virus, measles virus, parainfluenza 3 virus, cytomegalovirus (CMV), Epstein-Barrvirus (EBV), adenovirus, and bacillus Calmette-Guérin (BCG) lead to death. Affected infants also lack the ability to reject foreign tissue and are therefore at risk for graft versus host disease (GVHD) from maternal immunocompetent T cells crossing the placenta, or from T lymphocytes in nonirradiated blood products or allogeneic stem cell transplantation.

Because all molecular types of SCID lack T cells, infants with SCID have lymphopenia (<2,500/mm^3) that is present at birth, indicating that the condition could be diagnosed in all affected infants if white blood cell counts with manual differential counts were routinely performed on all cord bloods and the absolute lymphocyte count calculated.

TREATMENT.

SCID is a true pediatric emergency. Unless immunologic reconstitution is achieved through stem cell transplantation, death usually occurs during the 1st year of life and almost invariably before 2 yr of age. If diagnosed at birth or within the 1st 3.5 mo of life, >95% of cases can be treated successfully with HLA-identical or T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cell transplantation without the need for pretransplant chemoablation or post-transplant GVHD prophylaxis.

Disorders of Phagocyte Function

Neutrophils are particularly important in protecting the skin, mucous membranes, and lining of the respiratory and gastrointestinal tracts as part of the 1st line of defense against microbial invasion.

LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency 1 (LAD-1) and 2 (LAD-2) are rare autosomal recessive disorders of leukocyte function. LAD-1 affects about one per 10 million individuals and is characterized by recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia.

CLINICAL MANIFESTATIONS.

Patients with the severe clinical form of LAD-1 express <0.3% of the normal amount of the β_2-integrin molecules, whereas patients with the moderate phenotype may express 2–7%. Children with severe disease present in infancy with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. They may have a history of delayed separation of the umbilical cord, usually with associated infection (omphalitis) of the cord stump. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms. The ulcers heal slowly, require months of antibiotic treatment, and often require plastic surgical grafting. Severe gingivitis similar to what occurs in patients with profound neutropenia is common, with early loss of primary and then secondary teeth.

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 130) and include *Staphylococcus aureus* and enteric gram-negative organisms such as *Escherichia coli.* These patients are also susceptible to fungal infections such as *Candida* and *Aspergillus.* The typical signs of inflammation such as swelling, erythema, and warmth may be absent. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues. Despite the paucity of neutrophils within the affected tissue, the circulating neutrophil count during infection typically exceeds 30,000/µL and can surpass 100,000/µL. During intervals between infections, the peripheral blood neutrophil count may chronically exceed 12,000/µL.

LABORATORY FINDINGS.

The diagnosis of LAD-1 is established most readily by **flow cytometric**.

Assessment of neutrophil and monocyte adherence, aggregation, chemotaxis. Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis. Some patients, however, have impaired T lymphocyte–dependent antibody responses that can be demonstrated by suboptimal responses to repeat vaccination with tetanus toxoid, diphtheria toxoid, and poliovirus.

The diagnosis of LAD-2 is established by demonstrating the lack of sialyl Lewis X on the neutrophil.

TREATMENT.

Treatment of LAD-1 depends on the phenotype as determined by the level of expression of functional CD11/CD18 integrins. Early **allogeneic stem cell transplantation** is the treatment of choice for severe LAD-1 associated with complete absence of the CD11/CD18 integrins.

Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim-sulfamethoxazole and should have close surveillance to identify infections early.

Broad-spectrum antibiotics are indicated for empirical therapy when infection occurs. Determination of the etiologic agent by culture and biopsy is important because of the prolonged antibiotic treatment required for indolent infections.

Some patients but not others responded to fucose supplementation, which induced a rapid reduction in the circulating leukocyte count and appearance of the sialyl Lewis X molecules accompanied by marked improvement in leukocyte adhesion.

PROGNOSIS.

The severity of infectious complication correlates with the degree of β_2-integrin deficiency. Patients with severe deficiency may die in infancy, and those surviving infancy have a susceptibility to severe life-threatening systemic infections. Patients with moderate deficiency have infrequent life-threatening infections and relatively long survival.

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is characterized by the ability of neutrophils and monocytes to ingest but their inability to kill **catalase-positive microorganisms** because of a defect in the generation of microbial oxygen metabolites. CGD is a rare disease with an incidence of four to five per million individuals, caused by genes affecting one X-linked and three autosomal recessive chromosomes.

CLINICAL MANIFESTATIONS.

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. Any patient with recurrent or unusual pneumonia, lymphadenitis, hepatic or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or unusual infections with catalase-positive organisms *(S. aureus)* requires evaluation.

The onset of clinical signs and symptoms may occur from early infancy to young adulthood. The attack rate and severity of infections are exceedingly variable. The most common pathogen is *S. aureus,* although any catalase-positive microorganism may be involved. Other organisms frequently causing infections include *Serratia marcescens, Burkholderia cepacia, Aspergillus, Candida albicans, Nocardia,* and *Salmonella.* Pneumonia, lymphadenitis, osteomyelitis, and skin infections are the most common illnesses encountered. Bacteremia or fungemia occur but are much less common than focal infections. Patients may suffer from the sequelae of chronic infection, including anemia of chronic disease, poor growth, lymphadenopathy, hepatosplenomegaly, chronic purulent dermatitis, restrictive lung disease, gingivitis, hydronephrosis, and pyloric outlet narrowing. Perirectal abscesses and recurrent skin infections, including folliculitis, cutaneous granulomas, and discoid lupus erythematosus also suggest the possibility of CGD. **Granuloma formation** and inflammatory processes are a hallmark of CGD and may be the presenting symptoms that prompt testing for CGD if they cause pyloric outlet obstruction, bladder outlet or ureter obstruction, and rectal fistulae or intestinal granulomas simulating Crohn disease.

LABORATORY FINDINGS.

For screening of CGD, the nitroblue tetrazolium (NBT) dye test is widely used; it is rapidly being replaced by the more accurate **flow cytometry** test using dihydrorhodamine 123 (DHR). .

TREATMENT.

Hematopoietic stem cell transplantation is the only known **cure** for CGD. Vigorous supportive care along with recombinant interferon (IFN)–γ is used before transplantation. As part of supportive care, patients with CGD should be given daily oral trimethoprim-sulfamethoxazole for prophylaxis of infections. Cultures must be obtained as soon as infection is suspected. Most abscesses require surgical drainage for therapeutic and diagnostic purposes. Prolonged use of antibiotics is often required. Granulocyte transfusions may be necessary if antibiotics are ineffective. If fever occurs without an obvious focus, it is advisable to consider the use of radiographs of the chest and skeleton as well as CT scans of the liver to determine if pneumonia, osteomyelitis, or liver abscesses are present. The cause of fever cannot always be established, and empirical treatment with broad-spectrum parental antibiotics is often required. The erythrocyte sedimentation rate (ESR) may be used to help determine the duration of antibiotic treatment.

Aspergillus infection requires treatment with amphotericin B. Corticosteroids may also be useful for the treatment of children with antral and urethral obstruction. Granulomas may be sensitive to low doses of prednisone (0.5 mg/kg/day); treatment should be tapered over several weeks