

Complimentary CME/CE Activity

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Target Audience

Oncologists, hematologists, immunologists, nurses,
and pharmacists

Activity Goal

To familiarize physicians, nurses, and pharmacists
with the latest developments in the field of immune
globulin intravenous (IGIV) therapy and the rele-
vance to patient care—specifically, key strategies
for diagnosing primary immunodeficiency disease
(PID) in patients with recurrent infections.

*This issue is part of a series of 4 continuing
education newsletters.*

Learning Objectives

After completing this activity, participants should be
better able to:

- Describe the clinical presentation patterns that
point to PID as a possible diagnosis.
- Use clinical findings to select appropriate screen-
ing tests for patients with suspected PID.
- Develop a management plan, including IGIV and
genetic counseling, for patients with PID.

Accreditation



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and Policies of the Accreditation Council for
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IGIV: Achieving Improved Patient Outcomes

Recognizing Primary Immunodeficiency Disease Early: A Case-Based Approach

For more than 2 decades, immune globulin intravenous (IGIV) has been a life-saving therapy for patients who lack primary humoral immunity. Although primary immune deficiency (PID) is thought to be rare, its true incidence and prevalence are not known because children and adults are not screened routinely for immune defects. Prevalence rates for diagnosed PID are estimated at 1 in 2000 children or 1 in 1200 persons in the United States regardless of age.¹ B-cell deficiencies account for more than 30% of PID cases, while combined humoral and cellular deficiencies account for about 20% to 30% of cases.²

PID often remains unrecognized for years after symptom onset. For patients diagnosed with PID during the 1970s, the average time from symptom onset to diagnosis was 7.0 years, and this situation has not improved.³ For patients diagnosed during the 2000s, an average of 9.9 years elapse from symptom onset to diagnosis.³ More than 80% of PID cases are diagnosed in patients <20 years of age.⁴ Early recognition of PID is critical to instituting lifesaving treatment and providing genetic counseling to families.² A high index of suspicion is required. Recurrent infection is the most common reason for suspecting PID, and 57% of PID patients report it was the reason for undergoing initial testing.³

This issue of IGIV: Achieving Improved Patient Outcomes is the third in a series of 4 continuing education newsletters on current trends in IGIV therapy. The case report highlights key strategies for recognizing PID in children with recurrent infection.

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Dr Shah: has no significant relationships to disclose.

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1. Study the newsletter.
2. Relate the content material to the learning objectives.

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The estimated time to complete this activity is 1 hour. Upon successful completion of the above requirements, CME/CE certificates will be mailed within 6 weeks of receipt of the evaluation form. CPE certificates will be generated online.

Release date: June 30, 2008

Expiration: Credit will be awarded for required materials received no later than June 30, 2009.

Case: Bill, A 4-Year-Old Boy With Recurrent Infections

History

- Recurring otitis media (beginning at age 9 months); responded to pressure-equalization (PE) tube placement (age 1 year)
- Pneumonia, right middle lobe (age 15 months) and left lower lobe (age 18 months)
- Recurring sinus infections (beginning at age 3 years) despite antibiotic therapy; bilateral maxillary and ethmoid sinus involvement on CT scan; transient response to maxillary sinus drainage and bilateral opening of osteomeatal complex
- Attendance at day care 2 days per week
- No history of passive smoking; no family history of allergies; no history of infection or allergy in older sister

Physical Findings

- Appearance: thin, no acute distress; weight in the 10th percentile, height in the 60th percentile
- Skin: clear, no rashes; ears: bilateral scarring of tympanic membranes; nose: nasal turbinates slightly erythematous and swollen, white-yellow secretions; pharynx: tonsils absent, white-yellow postnasal drainage; neck: absence of lymph nodes along sternocleidomastoid muscle; abdomen: hepatosplenomegaly or other palpable masses absent; chest auscultation: clear, no rales, rhonchi, or wheezing; other physical findings: unremarkable

Why should PID be suspected in Bill?

Clinical Presentation Patterns in PID

The clinical presentation of PID varies by the type of immune defect, but clinical symptoms may differ even among patients with the same defect.⁴ A history of infections that are persistent, recurrent, severe, unresponsive to treatment, or caused by unusual microbes is the hallmark of PID.^{2,4-6} However, increased exposure to pathogens (because of day care attendance or school-aged siblings), passive smoking, allergies (asthma, allergic rhinitis, and eczema), anatomic defects of the upper and lower airways, and gastroesophageal reflux also increase the risk of recurrent infections, even in children with normal immune function. For example, recurrent otitis media often is associated with eustachian tube dysfunction secondary to atopy, and recurrent or chronic sinusitis may be linked to poor sinus drainage due to defects in the sinuses.² A detailed history and physical examination can provide clues to an underlying immune defect.

History of Recurrent Infection

Common sites of infection in patients with immune deficiency include the middle ear, paranasal sinuses, lungs, gingivae, meninges, skin, internal organs, and blood.² Recurrent infections at 1 site generally indicate an anatomic abnormality rather than PID, but a history of several types of infections affecting various organ

systems may signal an underlying immune deficiency.^{2,5,6} Otitis media, sinusitis, pneumonia, gingivitis, meningitis, septicemia, skin infections, and abscesses (eg, of internal organs, lymph nodes, or muscle) may be associated with immune deficiency, but pharyngitis typically is not.²

The microbiology of the infection may indicate the nature of the immunodeficiency. Bacterial infections suggest underlying antibody deficiencies, while severe infections due to viruses, fungi, or other opportunistic organisms point to T-cell deficiencies. Recurrent infections with staphylococcal and other catalase-positive organisms may indicate phagocytic defects, and *Neisseria* infections characterize complement deficiencies.^{2,4}

Age at infection onset is also a good indicator of the immune defect. Children with B-cell deficiency, such as X-linked agammaglobulinemia (Bruton's disease), are usually infection-free until 7 to 9 months of age when protection from maternally-derived immunoglobulin G (IgG) is lost. Infections begin at a younger age, typically 4 to 5 months, in children with both T-cell and B-cell immunodeficiency.²

Family History

Because many PIDs are inherited as an autosomal recessive or X-linked disorder, a good family history is essential.² If parents are afflicted, an autosomal recessive disorder is likely. Presence of an autoimmune disorder

(such as pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, or autoimmune hematologic disease) in family members often signals common variable immunodeficiency or IgA deficiency. Unexplained early infant deaths from serious infection also should arouse suspicion.

Physical Findings

Although normal physical findings do not exclude PID, physical examination can detect signs of previous infections as well as anatomic features specific to various PIDs. If recurrent infections begin early in life, growth and development may be delayed, leading to failure to thrive. Children with PID (particularly those with significant T-cell impairment) may appear chronically ill and underweight.² Repeated pyogenic infections can result in permanent scarring. Tympanic membrane scarring due to chronic otitis media is typical of B-cell defects.²

Developmental embryologic abnormalities are associated with certain PIDs. Aplasia or dysplasia of the thymus is associated with T-cell immunodeficiency. Absence of lymphoid tissues is seen in X-linked agammaglobulinemia, while hypertrophy of lymphoid tissues could signify common variable immunodeficiency or autoimmune lymphoproliferative syndrome. Children with adenosine deaminase (ADA) deficiency often show characteristic skeletal abnormalities of the ribs and hips on x-ray.²

Case Commentary: Why Should PID Be Suspected in Bill?

Attending day care and having a school-aged sibling may have contributed to Bill's recurrent infections; however, the absence of allergies and tobacco smoking in his family—important risk factors for recurrent infections of the upper respiratory tract—should arouse suspicion. Multiple infection sites and the frequency and severity of the infections also indicate the possibility of PID as a cause of recurrent infection. Although Bill's otitis media responded to PE tube placement allowing drainage through the tympanic membrane, corrective sinus surgery provided only transient improvement. Onset of infection at age 9 months also points to possible PID.

Bill's tympanic membranes were scarred from chronic infection and inflammation. He had no detectable tonsil tissues or palpable lymph nodes along the cervical chain. This absence of tonsillar and lymphoid tissue and the scarred tympanic membranes strongly suggest an underlying immune deficiency.

Bill's recurrent bacterial infections of the sinopulmonary tissues indicate the need for a humoral immune workup. Screening should include quantitation of serum immunoglobulins and testing for

specific antibodies produced after natural exposure to viral respiratory pathogens or following vaccine immunization. Flow cytometry allows detection and quantitation of T- and B-cell subsets in peripheral blood, but does not provide information about their function.

Screening Tests

A complete blood cell (CBC) count and manual differential can identify or rule out many immune defects in children with suspected PID.⁶ The white blood cell count and differential also can be used to calculate the absolute neutrophil count to rule out neutropenia.² Selection of other tests should be based on the suspected abnormality in immune function; results would help determine the need for advanced testing and referral to an immunologist.²

If humoral immune dysfunction is suspected, serum levels of immunoglobulin isotypes and IgG subclasses as well as specific antibody responses to polysaccharides (eg, isohemagglutinins to ABO blood group antigens [IgM], unconjugated pneumococcal vaccine) and proteins (eg, influenza B vaccine, diphtheria toxoid, tetanus toxoid) should be measured. B-cell numbers and markers can be quantified with flow

cytometry.^{2,7} Assessment of specific antibody formation after vaccine administration is important because patients with B-cell deficiency may have normal serum levels of total immunoglobulin and IgG subclasses but still fail to produce specific antibodies to bacterial or common viral pathogens.²

Cellular immune dysfunction is evaluated by lymphocyte/mononuclear cell quantitation (eg, T-cell numbers and subsets [CD4, CD8] with flow cytometry using monoclonal antibody methods) and functional assays of lymphocyte proliferative responses to mitogens and specific antigens.^{2,7} A total lymphocyte count below 2500/ μ L in a young child is significant for possible T-cell immunodeficiency.²

If complement dysfunction is suspected, complement hemolytic assays (CH50 for the classic pathway and AH50 for the alternative pathway) should be performed.^{2,7} CH50 will be immeasurable in patients with congenital complement deficiency.² Phagocyte dysfunction is evaluated by the absolute neutrophil count, morphologic assessment of circulating neutrophils, dihydrorhodamine assay by flow cytometry (for chronic granulomatous disease), and phagocytic assays.

Case: Bill, A 4-Year-Old Boy With Recurrent Infections

Laboratory/Imaging Findings

- CBC count and differential: normal
- Quantitative serum immunoglobulin analysis: IgG, 150 mg/dL; IgA, undetectable; IgM, 10 mg/dL
- Specific antibody assays: tetanus toxoid: negative; viral respiratory pathogens (respiratory syncytial virus, mycoplasma, and influenza A and B): negative; pneumococcal polysaccharide serotypes: negative; repeated antibody assays 4

weeks after immunization with tetanus toxoid and conjugated and unconjugated pneumococcal vaccines: negative for these antibodies

- Flow cytometry for T- and B-cell subsets: T-cell numbers and subsets (CD4 and CD8) normal; B cells absent (<1%)
- Repeated sinus limited CT scan: opacification of left maxillary sinus and both ethmoid sinuses; chest x-ray film and high-resolution chest CT scan: normal

What is the diagnosis? What should be done next?

Management

Preventing infection, prolonging life, and improving quality of life are the goals of therapy for PID diseases.⁴ Antibiotic therapy to treat and prevent infections is a key component of management. In children with significant T-cell defects, antibiotic prophylaxis against *Pneumocystis jiroveci* (*carinii*) may help prevent infections.² Because of the risk of vaccine-induced infection, live-attenuated vaccines (such as oral

polio, varicella, and *bacillus* Calmette-Guérin) are contraindicated in patients or family members with suspected or diagnosed antibody or T-cell deficiency.

Treatment options for PID diseases include immunoglobulin replacement with IGIV (for antibody deficiencies, except IgA deficiency), enzyme replacement with ADA conjugated to polyethylene glycol (for ADA deficiency), and bone marrow and stem cell transplantation.² Gene

therapy for immune deficiency disorders is in clinical trials.

The genetic basis of many immune deficiency disorders is known.² Thus, genetic testing, carrier detection, and counseling usually are recommended for affected families. Counseling on carrier detection and prenatal diagnosis should be offered to families with X-linked disorders. Some PID diseases such as ADA deficiency, leukocyte adhesion deficiency, and bare

lymphocyte syndrome can be diagnosed prenatally.

**Case Commentary:
What Is the Diagnosis? What Should Be Done Next?**

Bill's history of recurrent infections and lack of tonsil tissue and cervical lymph nodes pointed to a B-cell deficiency. Further testing revealed severe hypogammaglobulinemia, absence of specific antibodies, and absence of

B cells. These findings are consistent with a diagnosis of X-linked agammaglobulinemia, or Bruton's disease.

Referral to a clinical immunologist for initiation of IGIV therapy and genetic testing and counseling is warranted. A thorough family history should be obtained to determine evidence of an inheritance pattern. Bill and his mother should be tested for mutations in the Bruton's tyrosine kinase gene, although approximately 20% of patients have

de novo mutations. If the mother is a carrier, Bill's sister also should be tested.

Conclusions

Early detection is possible for most PID diseases. Increased vigilance and familiarity with different clinical presentation patterns of PID are critical. Treatment initiated early in the course of disease helps reduce morbidity, disability, and mortality.

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