AAOA allergy primer: immunodeficiency

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Background: Primary immunodeficiency is rare but should be considered in patients who present to the otolaryngologist with recurrent, severe, or treatment refractory infections.

Methods: Recent literature and consensus statements on immunodeficiency were reviewed for clinically important information of relevance to otolaryngologists.

Results: The most common and most relevant immunodeficiencies are humoral deficiencies with inadequate antibody production or an impairment in the production of specific antibody after antigen exposure. For otolaryngologists the most important immunodeficiencies include immunoglobulin A (IgA) deficiency, common variable immunodeficiency (CVID), and specific antibody deficiency. Simple screening tests can be used by the otolaryngologist to exclude the most common immunodeficiencies. The general treatment approach to patients with these immunodeficiencies includes airway hygiene, early and aggressive treatment

of infections, immunization, and antibody replacement therapy.

Conclusion: By virtue of their scope of practice, otolaryngologists are in a position to recognize and initiate the diagnostic workup of patients with immunodeficiency. Patients with a diagnosed primary immunodeficiency are best managed in a multidisciplinary manner with close cooperation among the otolaryngologist, immunologist, and other specialists that are involved in treating these multisystem diseases. © 2014 ARS-AAOA, LLC.

Key Words:
primary immunodeficiency; humoral immunodeficiency; antibody deficiency; rhinosinusitis

The primary immunodeficiencies are a broad group of genetic diseases that predispose to chronic and recurrent infection as well as autoimmune and neoplastic disease. Recurrent sinopulmonary infections are the most prevalent infections among patients with primary immunodeficiency. One study of patients referred to an immunology clinic for evaluation of immune deficiency revealed that the most common clinical manifestations included chronic sinusitis, chronic bronchitis, otitis media, pneumonia, and acute sinusitis.[1] Another study showed that 67% of patients with refractory chronic sinusitis who were referred to an immune dysfunction clinic and underwent functional antibody testing had defective functional antibody responses.[2] Otolaryngologists are thus on the "front line" in the detection and treatment of immunodeficiency and should be

prepared to initiate the diagnostic workup for suspected immunodeficiency. Primary immunodeficiency should be distinguished from medication induced immunodeficiency as well as secondary immunodeficiency due to viruses such as human immunodeficiency virus (HIV). This article focuses exclusively on the primary immunodeficiencies and aims to provide practical information about the characteristics of major immune deficiencies that are associated with ear, nose, and throat (ENT) infections, discuss the laboratory evaluation of patients with suspected immunodeficiency, and describe the general treatment approach for these conditions.

Immunodeficiency

Immunodeficiencies are classified by the immunologic mechanisms that are disrupted. There may be deficiencies in antibody production, cell-mediated immunity, or a combination of antibody and cell-mediated immunity. Innate immune mechanisms may also be deficient, eg, granulocyte dysfunction and deficiencies of the complement pathway, though these are not as relevant for the otolaryngologist, in part because of their rarity. Immunodeficiencies can also be categorized by the specific molecular and genetic defect

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involved, though genetic testing is not yet commercially available for most conditions. Over 120 genes have been identified that lead to primary immunodeficiency and there are more than 150 clinical phenotypes described.[3] From a clinical standpoint, the phenotype and specific immune component derangement are most relevant.

Primary immunodeficiency is rare in the general population. However, with the advent of new diagnostic testing modalities and improved awareness, the prevalence appears to be increasing.[4] Estimates of the overall prevalence of primary immunodeficiency range from 1:700 for selective immunoglobulin A (IgA) deficiency to 1:200,000 for chronic granulomatous disease (a neutrophil function disorder).[3] Among the primary immunodeficiencies, humoral (antibody) immunodeficiency is the most common and makes up approximately 50% of primary immunodeficiency cases.[3] While we know that recurrent respiratory infections are among the most common clinical presenting features of the primary immunodeficiencies, the prevalence of immunodeficiency in patients with recurrent acute otitis media, recurrent acute sinusitis, or chronic sinusitis is unknown. Given the unknown prevalence of immunodeficiency in patients who might present to an otolaryngologist, the clinician must remain vigilant to the possibility of immunodeficiency in patients with troublesome ENT infections.

Diagnosis

The diagnosis of immunodeficiency begins with a thorough history. Patients with immunodeficiency usually suffer from common infections. However, these common infections are frequently recurrent, at a rate that exceeds what is expected in an age-matched population. Infections may be unusually persistent despite appropriate treatment, or they may be unusually severe. Sometimes immunodeficiency comes to light because of infection with a rare organism. As these are genetic disorders, the family history is extremely important; although many cases of immunodeficiency go undiagnosed, a previous family history of recurrent or severe infections can point to the diagnosis. Patients with primary immunodeficiency are also susceptible to a variety of autoimmune or otherwise immune-mediated diseases. These include systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, celiac disease, and ulcerative colitis. A history of these conditions may provide further diagnostic clues that point to an immune system derangement.[3] Examples of warning signs for primary immunodeficiency include: >8 new ear infections in 1 year; >2 "serious" sinus infections in 1 year; an infection that fails to respond to 2 months of appropriate antibiotic treatment; more than 2 episodes of pneumonia in 1 year; recurrent deep skin or organ abscesses; persistent thrush in children over the age of 1 year; need for treatment with intravenous (IV) antibiotics to clear an infection; more than 2 deep-seated infections; and a family history of primary immunodeficiency.[5] Other examples of a concerning history include more than 4 courses of antibiotics per year in children and more than 2 in an adult;

4 new ear infections per year in patients over the age of 4 years; 2 episodes of pneumonia at any point in time; 3 episodes of bacterial sinusitis in 1 year, and a need for prophylactic antibiotics to prevent infection.[6]

Reliance on patient history alone is not satisfactory, however. A patient-reported episode of "pneumonia" should be further investigated with examination of any corroborating radiologic or laboratory data. A patient history of "recurrent sinusitis" should lead to in-depth questioning about the patient's symptoms, duration of illness, and treatment rendered. Many "sinus infections" are simply viral upper respiratory infections (URIs) or exacerbations of chronic rhinitis. Additionally, a variety of other conditions such as adenoid hypertrophy, allergic rhinitis, cystic fibrosis, and ciliary dyskinesia can be a cause for recurrent ENT infections. Physical examination, endoscopy, cultures, and radiologic studies are useful to document the presence of infection and may sometimes reveal stigmata of immune deficiency (eg, absent tonsils in a patient with agammaglobulinemia). After a thorough investigation, if suspicion of immunodeficiency remains then the next step in evaluation is to perform a screening battery of laboratory testing. Abnormal test results should prompt referral to an immunologist for a more extensive workup and to secure a diagnosis. If screening tests are normal, then further testing may not be necessary.

"Common" immunodeficiencies that are relevant for otolaryngology
Selective IgA deficiency

Selective IgA deficiency is the most common primary immunodeficiency. This condition may affect up to 1:700 individuals.[3] Interestingly, 90% of affected individuals are asymptomatic. Patients with selective IgA deficiency suffer from recurrent respiratory and gastrointestinal (GI) tract infections that may be viral or bacterial. Selective IgA deficiency is associated with atopy and affected individuals often suffer from the clinical manifestations of allergic disease. Autoimmune disease and malignancy are also more prevalent in IgA deficiency. The diagnosis of selective IgA deficiency is made with detection of absent or negligible serum IgA levels. Serum IgA levels rise with age. Therefore, low levels in young children do not necessarily indicate a problem. Affected individuals usually have normal IgG and IgM levels, though on occasion there may be some reduction in a particular IgG subclass as well as impaired specific antibody formation. Primary selective IgA deficiency should be distinguished from drug-induced IgA deficiency because a variety of medications can cause a secondary IgA deficiency. These include phenytoin, carbamazepine, valproic acid, sulfasalazine, gold, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs (NSAIDs).[3] There is no specific remedy for IgA deficiency. The treatment approach consists of nasal toilet, aggressive treatment of atopic disease (including the use of

allergen-specific immunotherapy), aggressive treatment of infections, and in some cases antibiotic prophylaxis.

IgG subclass deficiency

IgG subclass deficiency is a controversial diagnosis. It is not uncommon for otherwise normal individuals to have 1 or more IgG subclasses that fall below the normal range on standard testing. IgG4 is frequently low or undetectable.[7] However, some individuals with IgG subclass deficiency have an impairment in specific antibody response and will suffer from recurrent sinopulmonary and other infections. A diagnosis of IgG subclass deficiency is made with a determination that 1 or more IgG subclasses is greater than 2 standard deviations below the age-adjusted mean. In addition, specific antibody response testing should be performed to secure the diagnosis. In general, total IgG and IgM levels are normal in these individuals, though on occasion the IgA level may be low.[3]

Common variable immunodeficiency

The predominant clinical manifestation of common variable immunodeficiency (CVID) is recurrent sinopulmonary infection with encapsulated or atypical bacteria. As its name implies, CVID can be quite variable. More than 4 different genetic defects have been implicated in individuals with this clinical condition. CVID is considered to be a humoral immunodeficiency but T cell defects may also sometimes be seen. Approximately 1:7500 individuals may be affected with CVID, making this 1 of the more common primary immunodeficiencies.[3] The symptoms of CVID begin early in life and most patients will have clinical manifestations prior to adulthood. However, diagnosis often comes late and most individuals are not diagnosed until well into adulthood.[8] This is worrisome because in addition to recurrent infections, patients with CVID have a variety of other multisystem disorders and an increased risk of malignancy. Patients with CVID have a 40-fold to 300-fold increased risk of developing B cell non-Hodgkin's lymphoma and a 10-fold increased risk of gastric cancer.[3] Up to 25% of CVID patients have GI disease including lymphonodular hyperplasia, inflammatory bowel disease, malabsorption syndromes, Giardia infections, or bacterial enteritis. One fifth of CVID patients have an associated autoimmune disease such as immune thrombocytopenia, autoimmune hemolytic anemia, arthritis, and vasculitides.[3] Up to one third of CVID patients may develop a lymphoproliferative disorder. These include splenomegaly, intestinal lymphoid hyperplasia, as well as abdominal, mediastinal, or peripheral lymphadenopathy.[3] Therefore, an early and accurate diagnosis is critical so that these other conditions may be recognized and treated promptly.

Patients with CVID have a variable reduction in more than 1 immunoglobulin class including IgA, IgG, or IgM. These levels may wax and wane over time. Because of this variability, testing may be need to be repeated on multiple occasions. To secure the diagnosis, an IgG level more than 2 standard deviations below the mean normal value is required. Additionally, the detection of impaired specific antibody formation is required. The general treatment approach for CVID includes aggressive treatment of infections, antibiotic prophylaxis, and immunoglobulin replacement therapy.

Specific (polysaccharide) antibody deficiency

Specific antibody deficiency is a relatively newly described entity that may be 1 of the most challenging immunodeficiencies to identify. The prevalence in the general population is unknown, but 1 study detected a high prevalence of specific antibody deficiency in patients with refractory chronic sinusitis.[2] These individuals have normal levels of IgG, IgA, IgM, and IgG subclasses. The specific immune defect is an abnormal IgG antibody response to polysaccharide antigens.[9] Therefore, in the face of normal screening immunoglobulin testing, the only way to secure this diagnosis is to perform prevaccination and postvaccination titers for polysaccharide vaccines such as pneumococcus. As with the other immunodeficiencies, early and aggressive treatment of infections and prophylactic antibiotics may be employed. In severe cases immunoglobulin replacement therapy may be indicated.

Transient hypogammaglobulinemia of infancy

Transient hypogammaglobulinemia of infancy (THI) is a condition in which infants and young children have a delayed production of antibodies in the first 3 years of life. These individuals may suffer from recurrent bacterial, viral, and sinopulmonary infections. IgG levels fall below the 5th percentile for age, but there is a normal response to vaccines. Therefore, response to vaccines is used to secure the diagnosis and differentiate THI from other more serious conditions.[7] The treatment approach consists of early and aggressive antibiotic treatment and supportive care. Fortunately, this condition resolves with maturation of the immune system.

Agammaglobulinemia

Individuals with agammaglobulinemia suffer from early severe infections. In particular, these individuals experience recurrent otitis, sinusitis, and pneumonia with encapsulated bacteria in the first 2 years of life. They are also susceptible to viral infections of the central nervous system. Several genes have been implicated. An X-linked form of the disease (which is the most common), is due to a defect in the Bruton tyrosine kinase protein. Multiple genes involved in B cell maturation have been implicated in autosomal recessive agammaglobulinemia.[3] Individuals with agammaglobulinemia have very low or absent immunoglobulin levels, very low or absent B cells, and absent lymph nodes and tonsils. In some cases milder clinical phenotypes of agammaglobulinemia may have overlapping clinical and laboratory characteristics with CVID.

Laboratory evaluation for suspected humoral immunodeficiency

Laboratory diagnosis of primary immunodeficiency begins after a thorough evaluation points to the possibility of immunodeficiency. In situations where there is high clinical suspicion for immunodeficiency, simple screening laboratory testing can be performed to exclude the most common diagnoses. If there are any abnormalities detected on this screening workup then further testing can be performed or the patient can be referred to an immunologist.

The screening tests for humoral immunodeficiency consist of a complete blood count as well as serum levels of IgA, IgG, IgM, and IgG subclasses (optional). The next step in screening testing is to obtain IgG titers for antigens to which the patient should have mounted a response either from previous infection or immunization. IgG titers for tetanus, diphtheria, mumps, pneumococcus, Haemophilus influenza type B, and isohemagglutinins provide evidence that the patient's humoral immunity is intact. If these tests are normal, then no further workup is required. The confirmation of humoral immunodeficiencies (with the exception of IgA deficiency) often requires demonstration of an impaired specific antibody response. This sort of testing is considered to be crucial for the diagnosis of CVID, specific antibody deficiency, THI, and clinically significant IgG subclass deficiency. The procedure for testing specific antibody response is relatively simple: the testing begins with serum IgG titers for pneumococcal serotypes that are present in pneumococcal vaccines (eg, Pneumovax). If >70% of the serotypes are in the protective range (50% for children), then specific antibody impairment is unlikely and no further testing is necessary. However, if a significant number of titers are low, then the patient is vaccinated and 4 to 8 weeks later the titers are drawn again. If specific antibody formation is intact, one should see a 2-fold to 4-fold increase in any vaccinated serotype that was low on the original IgG titer testing. For adults, >70% of the serotypes should respond; an acceptable level in children is 50%.[3] Even in the presence of intact humoral immunity some titers may not show the expected increase, and the interpretation of post-vaccination titers may be challenging because of difficulty interpreting the results and differences among the available vaccines.[7] If laboratory evaluation points to a humoral immunodeficiency, further testing such as flow cytometry to count B cells or genetic testing can be performed.

Laboratory evaluation for other immunodeficiencies

Although not specifically highlighted in this work, a wide variety of cellular, granulocyte, and complement deficiencies may lead to recurrent ENT infections. The screening tests for cellular immunodeficiency consist of a complete blood count (CBC) with differential looking at absolute lymphocyte counts, HIV testing, and cutaneous delayed hypersensitivity testing. Delayed hypersensitivity testing is performed with intradermal tests against tetanus, monilia, or mumps antigen. A positive response is a 2-mm to 5-mm induration that is present at 48 to 72 hours. If this screening test testing is all normal then further diagnostic evaluation is usually not indicated. Abnormal screening tests may lead to further diagnostic testing that includes flow cytometry for specific T cell populations, assessment of in vitro lymphocyte proliferation response to various mitogens and antigens, enzyme assays, and the natural-killer (NK) cytolysis assay.[3]

Screening tests for granulocyte immunodeficiency look at the populations of neutrophils as well as their function. This is accomplished with an absolute neutrophil count as well as tests of oxidative function of the neutrophils.[3] Abnormal results should prompt additional testing and immunology consultation.

The complement system can be tested with 2 simple assays. The CH 50 assay assesses the classical complement activation pathway. This test of total complement activity measures the capacity of serum to lyse a standard preparation of sheep red blood cells coated with anti-sheep erythrocyte antibody. the AH 50 assay tests the alternative pathway via complement mediated lysis of rabbit erythrocytes. An abnormal result should prompt specific testing of C3 and C4, C1q and C1 esterase inhibitor.[3]

Treatment options for primary immunodeficiency

A wide variety of treatment approaches are available for the treatment of primary immunodeficiency. Some of these, such as upper and lower airway hygiene, early aggressive treatment of infections, and antimicrobial prophylaxis and immunization, are common to all of the primary immunodeficiencies. Some conditions may be amenable to antibody replacement therapy, and a variety of more advanced treatment approaches are employed in specific (usually rare) conditions. These include stem cell transplantation, gene therapy, and cytokine therapy. Surprisingly, immunization is recommended for individuals with primary immunodeficiency. The rationale for immunization is that some (albeit small) amount of protection may be obtained in some individuals who do respond to immunization. Inactivated or subunit vaccines should be administered according to routine schedules. However, it is very important to note that no live vaccines should be administered to patients with immunodeficiency. These include oral polio; measles, mumps, and rubella (MMR); oral typhoid; varicella; and yellow fever vaccines.[3] Antimicrobial prophylaxis for patients with primary immunodeficiency follows from the standard regimens that have been used in the past for otitis media. Acceptable antimicrobial prophylaxis regimens include amoxicillin 20 milligrams per kilogram (mg/kg) per day, sulfamethoxazole 50 mg/kg per day, or azithromycin 10 mg/kg weekly.

Immunoglobulin replacement therapy is considered to be beneficial in patients who have absent B cells or who have hypogammaglobulinemia with impaired specific antibody production. Immunoglobulin replacement therapy is also considered to be beneficial in individuals who have normogammaglobulinemia but impaired specific antibody production. From a practical standpoint this means that individuals with CVID, specific antibody deficiency, IgG subclass deficiency with impaired antibody response, or agammaglobulinemia should benefit from immunoglobulin replacement therapy. Immunoglobulin replacement is not considered to be beneficial in selective IgA deficiency or isolated IgG4 subclass deficiency.[10] Intravenous administration of immunoglobulin has the longest track record of success. Large amounts of immunoglobulin can be infused and dosing performed every 2 to 4 weeks. However, this approach results in significant time periods with a low IgG trough, and dose-related side effects are common. Additionally, this treatment approach requires frequent infusion visits for what is essentially a long-term treatment approach. In response to these limitations, subcutaneous immunoglobulin therapy has been developed. With this approach there is no need for intravenous access and individuals may self-administer the immunoglobulin at home. The subcutaneous route of administration results in gradual absorption that both reduces the side effects of administration and reduces the troughs that may make individuals susceptible to infection. Subcutaneous immunoglobulin may be dosed every 1 to 2 weeks.[3]

Conclusion

Primary immunodeficiency is rare but should be considered in patients who present to the otolaryngologist with recurrent, severe, or treatment refractory infections. The most common and most relevant immunodeficiencies are humoral deficiencies with inadequate antibody production or an impairment in the production of specific antibody after antigen exposure. For otolaryngologists the most important immunodeficiencies include IgA deficiency, CVID, and specific antibody deficiency. Simple screening tests can be used by the otolaryngologist to exclude the most common immunodeficiencies. The general treatment approach to patients with these immunodeficiencies includes airway hygiene, early and aggressive treatment of infections, immunization, and antibody replacement therapy. Patients with a diagnosed primary immunodeficiency are best managed in a multidisciplinary manner with close cooperation among the otolaryngologist, immunologist, and other specialists that are involved in treating these multisystem diseases. 🕊

References

1. Yarmohammadi H, Estrella L, Doucette J, et al. Recognizing primary immune deficiency in clinical practice. *Clin Vacc Immunol.* 2006;13:329–332.

2. Alqudah M, Graham SM, Ballas ZK. High prevalence of humoral immunodeficiency patients with refractory chronic rhinosinusitis. *Am J Rhinol Allergy.* 2010;24:409–412.

3. Bonilla FA, Bernstein IL, Khan DA, et al.; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* 2005;94:S1–S63.

4. Joshi AY, Iyer VN, Hagan JB, et al. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. *Mayo Clin Proc.* 2009;84:16–22.

5. Wasserman RL, Manning SC. Diagnosis and treatment of primary immunodeficiency disease: the role of the otolaryngologist. *Am J Otolaryngol.* 2011;32:329–337.

6. De Vincentiis GC, Sitzia E, Bottero S, Giuzio L, Simonetti A, Rossi P. Otolaryngologic manifestations of pediatric immunodeficiency. *Int J Pediatr Otorhinolaryngol.* 2009;73(Suppl 1):S42–S48.

7. Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2012;130(3 Suppl):S1–S24.

8. Oskenhendler E, Gerard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. *Clin Infect Dis.* 2008;46:1547–1554.

9. Cheng YK, Decker PA, O'Byrne MM, Weiler CR. Clinical and laboratory characteristics of 75 patients with specific polysaccharide antibody deficiency syndrome. *Ann Allergy Asthma Immunol.* 2006;97:306–311.

10. Orange JS, Hossny EM, Weiler CR, et al.; Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol.* 2006;117(4 Suppl):S525–S553.