

Otitis Media as a Presenting Complaint in Childhood Immunodeficiency Diseases

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Otitis media is one of the most common childhood infections and may result from a variety of underlying problems. Suspicion of immunodeficiency should increase when ear infections are frequent; suppurative; unresponsive to antibiotics; caused by unusual organisms; or seen in the context of other frequent infections, severe eczema, or failure to thrive. Humoral immune deficiencies, particularly with an inability to make antibody to encapsulated organisms, are the immunodeficiencies most likely to cause increased otitis media. Immune system evaluation should concentrate on humoral immunodeficiency disorders, but the presenting history and physical findings also should be considered when designing the work-up. Treating the underlying immune deficiency is usually necessary to adequately control the ear infections.

Introduction

“If you want to see a good number of very abnormal eardrums very quickly, hang around the Immunology Clinic for a few hours. All the patients there have ear problems.” That was a quote from one of our residents to a medical student wanting to see some ear pathology. That otitis media is associated with immunologic problems is appreciated by immunologists, primary care physicians, and parents alike. Otitis media is one of the most frequent reasons for referral to an immunologist. Eight or more new ear infections per year is presented as one of the 10 warning signs for primary immune deficiency on posters published by the Jeffrey Modell Foundation [1]. The most common head and neck manifestations of immunodeficiency disease are recurrent suppurative

otitis media, tonsillitis, sinusitis, rhinitis, and nasopharyngitis [2]. This article reviews the relationship between otitis media and immunodeficiency.

Otitis Media

Approximately one half of children have an episode of otitis media before their first birthday, and 80% have one by their third birthday. It occurs more frequently in boys than girls. Otitis media is the major reason cited for pediatric visits to primary care physicians or emergency departments. Physicians prescribe antibiotics more for children with otitis media than for any other reason. The disease causes infants, children, and their families great distress and accounts for at least \$3 to \$4 billion in health care bills each year [3,4].

Otitis media, defined as inflammation of the middle ear [5], usually presents in one of three forms: acute otitis media (AOM), otitis media with effusion, or chronic suppurative otitis media. AOM is self-limited, as it usually accompanies a viral upper respiratory infection. In young children, viral AOM often quickly leads to secondary complications such as bacterial otitis media [6]. The individual with bacterial AOM has “earache” pain that usually is accompanied by fever. Complications of bacterial otitis media include perforation of the tympanic membrane and progression to mastoiditis.

Otitis media with effusion is a collection of fluid that occurs within the middle ear space as a result of the negative pressure produced by altered eustachian tube function. Reasons for eustachian tube dysfunction include faulty anatomy, allergy, bacterial otitis media, or viral infections. Fluid in the middle ear sometimes contributes to conductive hearing impairment, as it interferes with the vibration of the eardrum. Long-term, ongoing presence of middle ear fluid can result in thickening of the effusion and increased likelihood of conductive hearing impairment.

Chronic suppurative otitis media involves an active bacterial infection with a persistent perforation in the tympanic membrane within the middle ear space for several weeks or more. Otorrhea is a frequent feature. Eustachian tube dysfunction is a common factor in chronic suppu-

rative otitis media. Hearing impairment secondary to middle ear effusion is common.

The increased incidence of otitis media in young children is often due to several factors: 1) the eustachian tube is structurally and functionally immature, 2) it is at a relatively more horizontal angle, or 3) the angle of the tensor veli palatini muscle and the cartilaginous eustachian tube renders the opening mechanism less efficient. Another factor that makes children more susceptible to otitis media is adenoidal hypertrophy. The adenoids are positioned in the back of the upper nasopharynx near the eustachian tubes, where enlargement can interfere with eustachian tube function. Many studies have correlated the incidence of AOM in children with various factors, such as nursing in infancy, bottle feeding when supine, parental smoking, diet, daycare exposure, and diesel exhaust emissions. Allergy often plays a role in increased middle ear infections [7••]. Extended breastfeeding is associated with a reduction in the number and duration of all otitis media infections [8]. Finally, immunodeficiency is a rare but important contributing factor to otitis media.

Middle Ear Immunology

Streptococcus pneumoniae and nontypeable *Haemophilus influenzae* are the most common bacterial causes of otitis media. Other common causes include *Moraxella catarrhalis*, *Mycoplasma* spp, and viruses [9•]. Sterile effusions occur in approximately 20% of cases.

Complex immunoregulatory mechanisms are maintained to respond to infectious organisms present in the middle ear [10,11]. Normally, mast cells are the predominant immunologic cell present. T and B lymphocytes accumulate in response to infection. Normally, there is minimal fluid in the middle ear. Effusions contain primarily secretory IgA with some IgG and IgM. Lack of IgA with the inability to generate a specific antibody response is associated with increased otitis media incidence [12]. Immunoregulatory cytokines identified in chronic otitis media include interleukin-2, interleukin-10, and transforming growth factor- β . Allergy-associated cytokines, such as granulocyte-macrophage colony-stimulating factor, also can be found [13].

The surfaces of the eustachian tubes and middle ear are lined with columnar epithelial cells with cilia. These epithelial surfaces are good places for biofilms to develop. Biofilms are complex, mucoid epithelial cell surface-attached organizations in which bacteria preferentially exist. Antibiotic penetration of the biofilm structure may be minimal, resulting in ongoing infection despite the infecting organism being sensitive to the chosen antibiotic. Biofilms have been shown to be involved in chronic otitis media, chronic tonsillitis, cholesteatoma, and device-associated infections [14].

Otitis Media and Immunodeficiency

Primary immunodeficiency results in recurrent infections, organ dysfunction, and autoimmunity. Otitis media is one of the most common infections in the presentation of immune deficiency. In a study of presenting diagnoses in patients with immune deficiency versus those who were found to have normal immune systems, only chronic sinusitis and chronic bronchitis were more common than otitis media. Yarmohammadi et al. [15••] noted in their study that 81 of 113 patients with immune deficiency had chronic otitis media, compared with 39 of 124 without immunodeficiency ($P < 0.001$). Haddad et al. [16] reviewed 75 hospitalized patients with immune deficiencies and found that 80% had infections of the ears, nose, and throat. Cultures showed that the infections were consistent with those caused by community-acquired organisms.

Studies of otitis media-prone children yield humoral immune abnormalities as compared with other children but little evidence of specific antibody defects. Veenhoven et al. [17] compared immunoglobulin levels in children with four or more episodes of otitis media in the previous year to those with fewer infections. Otitis-prone children had normal or increased serum IgA, IgM, IgG, and IgG1 levels compared with normal values for age, whereas the serum IgG2 levels were mostly in the lower normal range. The otitis-prone children showed significantly lower median and mean levels for all immunoglobulins compared with children with only two or three previous AOM episodes. When the same group looked at specific antibody levels, children with recurrent AOM actually showed higher antiphtheria and antitetanus antibody titers compared with controls. These children with recurrent otitis media had no differences in anti-*H. influenzae* type B and antimeasles antibody levels [18]. Prellner et al. [19] drew serial blood samples from 113 children from birth until age 3 years. They were divided into three groups: 13 developed recurrent AOM, an intermediate group had a few ear infections, and 29 remained healthy. Specific IgG antibodies against types 6A and 19F of *Pneumococcus*, but not against type 3, were significantly lower in the recurrent otitis media group than in the healthy children. The results suggested an association between preexisting low specific IgG antibody levels against otitis media-associated pneumococcal types and the development of recurrent otitis media.

Because otitis media is very common in children with normal immune systems, ear infections are expected to occur in children with immune deficiencies. Some immune deficiencies clearly are more prone to an increase in frequency and severity of otitis media than others. In our experience, humoral immune deficiencies are most likely to present with recurrent otitis media as the chief complaint. We have found that the more profound the inability to generate an antibody response to polysaccharide antigens, the more common and severe the ear pathology. Chronic suppurative otitis media is

more suggestive of an immune deficiency than frequent otitis media that resolves spontaneously or with antibiotic therapy (Table 1). Complications of otitis media, such as mastoiditis, also should trigger a concern for immunodeficiency.

Humoral Immune Deficiencies

Otitis media is an important finding leading to diagnosis of X-linked Bruton's agammaglobulinemia (XLA). Conley and Howard [20] described the clinical findings leading to the diagnosis of XLA in 82 patients with proven Bruton's tyrosine kinase mutations. Recurrent otitis was seen in most XLA patients who were more than 12 months old when diagnosed. In a registry of 201 patients with XLA, 70% had at least one episode of otitis, compared with 62% with at least one episode of pneumonia and 60% with at least one episode of sinusitis [21]. The history of recurrent otitis, when combined with markedly decreased or absent tonsils and cervical lymph nodes, should alert physicians to the diagnosis of XLA.

In our series of children diagnosed with common variable immune deficiency, otitis media was the second most frequent infection sustained, with 67% of children having recurrent disease. This exceeded the frequency of pneumonia (58%) [22••]. In a study of 248 adult patients with common variable immune deficiency, 98% presented with otitis media, sinusitis, or bronchitis [23].

Patients with impaired polysaccharide antibody deficiency with or without IgG subclass deficiency are very susceptible to otitis media [24–26]. Those patients with a combination of IgG subclass deficiency, IgA deficiency, and an inability to make antibody seem to fare worst [27]. Although sinopulmonary infections are associated with selective IgA deficiency, otitis media incidence is variable, especially in the absence of a selective polysaccharide antibody deficiency [28••]. Patients with IgA deficiency and the absence of nasal IgM-secreting cells had more recurrent acute rhinosinusitis, otitis media, and tonsillitis. These results suggest that IgM acts as a compensatory secretory immunoglobulin in the upper respiratory tract of some IgA-deficient patients [29].

Otitis media is associated with hyper-IgM syndrome. Using a national registry of patients with the X-linked hyper-IgM syndrome, Winkelstein et al. [30] described the clinical characteristics of 79 patients. All the patients had significant IgG deficiency, and most had IgA deficiency, but only one half had elevated IgM levels. Common clinical infections were pneumonia (81%), sinusitis (43%), recurrent otitis (43%), recurrent protracted diarrhea (34%), central nervous system infections (14%), sepsis (13%), cellulitis (13%), and hepatitis (9%). In addition to infections caused by encapsulated bacteria, such as those associated with otitis media, these patients often developed opportunistic infections.

Table 1. Immune deficiencies commonly associated with frequent otitis media

Bruton's agammaglobulinemia
Common variable immune deficiency
Polysaccharide antibody deficiency with or without IgG subclass deficiency
IgA deficiency with IgG2 subclass/polysaccharide antibody deficiency
X-linked hyper-IgM syndrome
Wiskott-Aldrich syndrome
Neutropenia: Kostmann's syndrome, autoimmune, cyclic
HIV infection
Delayed-onset adenosine deaminase deficiency

Complement Deficiencies

Complement deficiencies are generally associated with meningitis and bacteremia, particularly to encapsulated organisms such as *Neisseria* spp. Otitis media has been reported as a prominent feature in some complement deficiencies, such as factor 1 deficiency [31], C4b deficiency [32], C7 deficiency [33], C1r deficiency [34], and C2 deficiency [35].

Phagocytic Disorders

Some phagocytic defects are associated with recurrent or chronic otitis media. Bux et al. [36] described clinical findings in 143 patients with autoimmune neutropenia. The most common infections were benign bacterial infections of the skin, upper respiratory tract infections, and recurrent otitis media. Otitis media is not prevalent in patients with chronic granulomatous disease [37] but does occur with subsequent granulomatous complications [38]. We have seen an infant with chronic granulomatous disease whose primary presentation was upper airway obstruction due to granulomas in the posterior nasopharynx and subsequent otitis media. Rezaei et al. [39] described 26 patients with neutrophil disorders, 8 with cyclic neutropenia, 7 with Shwachman-Diamond syndrome, 6 with Kostmann's syndrome, and 5 with Chediak-Higashi syndrome. The most common infections, in descending order of frequency, were otitis media, abscesses, pneumonia, oral ulcers, acute diarrhea, cutaneous infections, oral candidiasis, and periodontitis. Less frequent infections were sinusitis, cystitis, conjunctivitis, meningitis, and osteomyelitis.

Cellular and Combined Disorders

Patients with severe combined immune deficiency sometimes develop otitis media but are more likely to present with early-onset severe infections, such as chronic diarrhea, interstitial pneumonitis, candidiasis, and failure

Table 2. Evaluation for immunodeficiency in patients with otitis media

Quantitative immunoglobulins (IgG, IgM, IgA)

Complete blood count with differential

Specific antibody titers

Diphtheria

Tetanus

Streptococcus pneumoniae IgG 12 serotype*Haemophilus influenzae* IgG

Isohemagglutinins

In some patients:

Total protein/albumin

IgE level

Antineutrophil antibodies

T-cell and B-cell subsets

Mitogens

CH50

HIV titer

to thrive. Some patients with adenosine deaminase deficiency have a delayed onset and present with frequent otitis media, sinusitis, pneumonia, and diarrhea but without opportunistic infections or growth failure [40,41]. Frequent, severe, and chronic otitis media is a common feature of Wiskott-Aldrich syndrome (WAS). Skoner [42] described a child who was not diagnosed with WAS until age 10 years and who presented with rhinitis, dermatitis, and otitis media more consistent with allergy than with a severe immune deficiency. Patients with WAS tend to have severe problems making antibody to polysaccharide antigens. However, Sullivan et al. [43] reported that 27% of 154 patients presented with the classic triad of thrombocytopenia with small platelets, recurrent otitis media, and eczema. In a description of infection sites in 40 patients with hyper-IgE syndrome, 75% had ear infections, and 5% required mastoidectomies [44]. This was more common than the classic infections of pneumatoceles, which 24 of 40 patients with hyper-IgE syndrome had.

HIV Infection

AOM occurs frequently in HIV-infected children. Shapiro and Novelli [45] reviewed 72 patients with vertically acquired HIV infection. Of these children, 44.4% presented with one or more episodes of otitis media. Six of these patients went on to suffer systemic complications secondary to middle ear pathology. Middle ear culture obtained from actively draining ears grew infectious organisms similar to those seen in immunocompetent children. Barnett et al. [46] compared experience with AOM of 28 HIV-infected children with that of 33 children who seroreverted to HIV antibody-negative status by age 18

months. The mean number of episodes per year of AOM for children who seroreverted decreased from 1.33 in the first year of life to 0.13 in the third year, whereas the mean number of episodes per year in HIV-infected children increased from 1.89 to 2.40. By age 3 years, all HIV-infected children had experienced one or more episodes of AOM, and 80% had experienced six or more, whereas 75% of children who seroreverted had experienced one or more episodes, and none had more than five. HIV-infected children with normal CD4 lymphocyte counts had a mean of 1.18 episodes of AOM in the first year of life, compared with 2.35 episodes in HIV-infected children with decreased counts. HIV-infected children with low CD4 counts had a nearly threefold increased risk of recurrent AOM.

Immunologic Evaluation of Children With Frequent Otitis Media

Infants and children with frequent episodes of otitis media should have other more common causes—such as anatomic abnormalities, allergies, and daycare exposure—investigated before initiating an immunodeficiency work-up. As with all immune evaluations, a careful history describing the frequency, severity, and duration of and response to antibiotics is essential. Ascertaining other associated infections, such as skin problems, diarrhea, organisms cultured, and growth problems, is helpful in developing a differential diagnosis. The clinician should look for physical examination findings, such as suppurative of the ears, eczema, rales, and evidence of failure to thrive.

In the child presenting primarily with recurrent otitis media for whom other causes have been ruled out, quantitative immunoglobulins, a complete blood count with differential, and specific antibody titers would be appropriate (Table 2). The antibody titers chosen should be based on the patient's age and immunization history. Patients with low antibody titers should be immunized and the titers remeasured in 3 to 4 weeks. A total protein and albumin measurement helps to determine if low gammaglobulin is due to a secondary immunodeficiency. Investigation of the T-cell lineage should be done in patients with a history of pneumonias, severe infections, eczema, or failure to thrive. If there has been a history of meningitis, complement studies should be included. If there is a history of unusual organisms, such as *Staphylococcus* spp or gram negatives, an evaluation of the patient's phagocytic oxidative metabolism would be appropriate. Any suggestion of risk factors for HIV should lead to an evaluation for that infection.

Management of Otitis Media Associated With Immunodeficiency

Management of otitis media in patients with underlying immune deficiencies tends to be similar to that in other

patients, with the exception that it tends to be more aggressive. Cultures from myringotomies with identification of infecting organisms and sensitivity assist in antibiotic selection; early initiation of antibiotic therapy; and, in some circumstances, hospitalization with intravenous antibiotics. Assistance from an otolaryngologist is often needed for patients with severe complications, such as mastoiditis, and for the placement of ear ventilation tubes.

In children without immune deficiency and a propensity to develop ear infections, long-term prophylactic antibiotics reduce the number of episodes of AOM per year from approximately three to about 1.5 [47]. Continuous or intermittent antibiotics have been used to decrease the number of infections in a variety of immune deficiencies associated with frequent otitis media, including WAS [48], common variable immune deficiency, specific antibody deficiency, IgA deficiency, chronic granulomatous disease [49], and C2 deficiency [50]. Prophylactic antibiotics are clearly not a substitute for antibody replacement with immunoglobulin. However, whereas continuous prophylactic antibiotics are frequently used in immunodeficient patients, an extreme paucity of clinical trials exists for their use in immune deficiency.

Those patients with hypogammaglobulinemia and evidence of an inability to make specific antibody should be placed on intravenous or subcutaneous immunoglobulin replacement. Patients with specific antibody deficiency who fail prophylactic antibiotics are particularly good candidates for immunoglobulin replacement. Patients with an immune deficiency for which there is a specific available treatment, such as polyethylene glycol–modified adenosine deaminase (PEG-ADA) or bone marrow transplant, should be treated appropriately.

Conclusions

Otitis media is a common problem in children and can be caused by a variety of underlying mechanisms. Suspicion of immunodeficiency should increase when the infections are frequent, severe, suppurative, unresponsive to antibiotics, caused by unusual organisms, or seen in the context of other frequent infections, severe eczema, or failure to thrive. Humoral immune deficiencies, especially those with specific inability to respond to encapsulated organisms, are the most likely to cause increased otitis media but also may be seen in certain phagocytic, complement, and combined disorders. Screening studies should concentrate on humoral disorders but should be tailored based on history and physical findings. Treatment involves aggressive use of antibiotics based on culture results. Otolaryngology consultation is frequently necessary. Treatment of the underlying immune deficiency is usually necessary to adequately control the ear infections.

Acknowledgments

The authors dedicate this article to James Montecalvo, a 26-year-old immune-deficient patient who presented with recurrent otitis media as a young child and who died on June 7, 2008, due to complications. His life is celebrated in that he was a beacon of hope and enthusiasm to everyone fortunate enough to know him. Also inspirational was his beautiful family and his great uncle, James Montecalvo, for whom he was named and who made it possible for James to receive his intravenous immunoglobulin on a regular basis. James' lifelong battle with immune deficiency and his triumph over two forms of cancer and many other illnesses have encouraged others in their trials never to give up.

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