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Otitis Media İn Immunodeficient Children

İmmün Yetmezlikli Çocuklarda Otitis Media

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Öz
İmmün yetmezlik, bağışıklık sistemini oluşturan elemanlarda gözlenen eksiklik veya fonksiyon bozukluğu ve buna bağlı gelişen klinik bulguları tanımlamaktadır. İmmün yetmezlik yaratan durumlar oldukça heterojen bir yapıda olup başlıca primer ve sekonder immün yetmezlikler olarak sınıflandırılmaktadır. Akut otitis media normal bağışıklık sistemine sahip çocuklarda en sık karşılaşılan enfeksiyonlardan biridir. İmmün yetmezliği olmayan çocuklarda da otitis medianın sıkça görülmesi immün yetmezlikli çocukların tanı almasını zorlaştırmaktadır. Pediatrik çağdaki rekürren ve şiddetli enfeksiyonların tedavilerinde zorluklar yaşanmaktadır. Otitis media geçiren bir çocukta bazı uyarıcı semptomlar altta yatan immünolojik bir eksikliği düşündürebilir. Bu derlemede immün yetmezliği olan çocuklarda görülen orta kulak hastalıkları, bu hastalıkların yönetimi ve tedavileri tartışılmıştır.
Anahtar Kelimeler: İmmün Yetmezlik, İmmün Yetmezlikli Çocuklar, Otitis Media

Abstract
Immunodeficiency refers to deficiencies or dysfunctions in the components of the immune system and the associated clinical manifestations. The conditions leading to immunodeficiency are highly heterogeneous and are primarily classified into primary and secondary immunodeficiencies. Acute otitis media is one of the most common infections in children with a normal immune system. However, the frequent occurrence of otitis media in children without immunodeficiency can complicate the diagnosis of immunodeficiency in affected children. Managing recurrent and severe infections in the pediatric population poses significant challenges. In a child with otitis media, certain indicative symptoms may suggest an underlying immunological deficiency. In this review, the middle ear diseases observed in children with immunodeficiency, as well as their management and treatments, are discussed.
Keywords: Immunodeficiency, Immunodeficient Children, Otitis Media

Introduction

Otitis media is an infectious process characterized by inflammation of the middle ear and associated cavities. Clinically, it generally presents in three forms. Among the most common clinical forms of otitis media are acute otitis media (AOM), otitis media with effusion (OME), and chronic suppurative otitis media (CSOM). Acute otitis media is usually a condition that develops secondary to self-limiting viral upper respiratory tract infections. While bacterial agents can lead to the development of infection in conjunction with viral agents, they can also occur as secondary infections following the initial viral infection (1,2).

In terms of prevalence, up to 50% of children will experience at least one episode of otitis media by the age of 1, and by age 3, up to 80% will have had at least one episode. Otitis media is more frequently observed in boys compared to girls and is a leading indication for antibiotic prescriptions in children. In particular, viral acute otitis media (AOM) in young children can quickly progress to secondary bacterial infections (3,4).

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Otitis media is more prevalent in children than in adults. Contributing factors include the incomplete structural and functional development of the Eustachian tube, increased incidence of adenoid hypertrophy, supine feeding practices in infants, passive smoke exposure, and allergies. Additionally, diseases associated with immunodeficiencies can further heighten susceptibility to AOM. Although immunodeficiencies are relatively rare risk factors for AOM, conditions that lead to local or systemic immunodeficiencies can contribute to recurrent otitis media and its complications.

Among the bacterial agents leading to the development of acute otitis media (AOM), *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common. Although less frequent, other agents that can cause AOM include *Moraxella catarrhalis* and *Mycoplasma spp* (5).

Middle Ear Immunity

In a healthy host, the natural immune system is adept at rapidly identifying and clearing pathogens from the middle ear. Histological analyses of the middle ear and associated structures, including the Eustachian tube and mastoid cells, reveal that upper respiratory epithelial cells, dendritic cells, and mast cells possess surface recognition receptors. These receptors facilitate the detection of bacterial surface molecules and the subsequent activation of various effector mechanisms. A decline in these immunological identification and protective functions can result in recurrent, persistent, or complicated inflammatory processes within the middle ear.

The middle ear mucosa employs a complex immune response mechanism to combat pathogenic microorganisms. Mast cells are the predominant immunological cells present in the middle ear mucosa. In response to infection, T and B lymphocytes are recruited. During otitis media with effusion, there is a predominant secretion of secretory IgA, accompanied by smaller quantities of IgG and IgM.

Given the frequent occurrence of otitis media in children with an otherwise normal immune system, the diagnosis of immunodeficiencies in such children may be delayed. It is crucial not to overlook specific triggering conditions in a child with otitis media. When these findings are present, a thorough evaluation for primary immunodeficiencies should be conducted.

Immunodeficiencies and Acute Otitis Media

Certain primary and secondary immunodeficiencies are notably associated with an increased frequency and severity of middle ear infections. Children with humoral immunodeficiencies often present with recurrent acute otitis media (AOM) as a primary complaint. The severity of ear pathology tends to correlate with the extent of impairment in producing antibody responses to polysaccharide antigens. Chronic suppurative otitis media in children should raise concern for potential underlying immunodeficiencies. Moreover, any complications arising from AOM in children should prompt a thorough evaluation for possible immunodeficiencies.

A study by Haddad et al. investigated 75 hospitalized patients with diagnosed immunodeficiency and found that 80% of these patients had an upper respiratory tract infection. Microbiological analysis of these infections identified the pathogens as community-acquired microorganisms, consistent with those typically found in healthy individuals (6).

Primary Immunodeficiency Disorders

Primary immunodeficiency disorders (PIDs) encompass a diverse group of over 130 conditions resulting from defects in the development and/or function of the immune system. Although PIDs are relatively rare, early diagnosis is essential to mitigate the associated morbidity and mortality. Delays in identifying and treating PIDs can lead to unnecessary antibiotic use and the performance of ineffective and often low-success-rate surgical interventions. Surgical procedures in these patients frequently exhibit low success rates and high complication rates (7).

Certain symptoms and clinical conditions should raise suspicion for a primary immunodeficiency. It is imperative that these indicative conditions are not overlooked.

Warning Symptoms for PID Diagnosis

The following symptoms should prompt consideration of primary immunodeficiency disorders (PIDs):

1. Eight or more new ear infections within one year
2. Two or more serious sinus infections within one year
3. Minimal response to antibiotics despite two or more months of treatment
4. Two or more episodes of pneumonia within one year
5. Failure to achieve normal weight gain or growth in an infant
6. Recurrent deep skin or organ abscesses
7. Persistent oral or cutaneous thrush beyond age one
8. Requirement for intravenous antibiotics
9. Two or more deep tissue infections
10. Family history of primary immunodeficiency (8).

AOM Characteristics Indicative of PID

Certain features of acute otitis media (AOM) may also suggest an underlying primary immunodeficiency. Clinicians should be particularly alert to:

- Onset of otitis media before 3-4 months of age
- Recurrence of AOM following antibiotic treatment
- Complications such as mastoiditis
- Invasive infections
- Recurrence despite the presence of ventilation tubes
- Need for recurrent tube insertions (9).

This section will review the most common primary immunodeficiency disorders that predispose individuals to otitis media. A summary of the diseases, their types, pathophysiology and treatments is presented in Table 1.

X-linked (Bruton's) Agammaglobulinemia (XLA)

X-linked (Bruton's) agammaglobulinemia is characterized by the complete absence of B lymphocytes and plasma cells. During the first six months of life, affected children may appear asymptomatic due to maternal antibodies. Post this period, they typically present with recurrent pyogenic upper respiratory tract infections, including those caused by *Pseudomonas aeruginosa*, *Haemophilus influenzae*, pneumococci, and other streptococci (10).

Clinically, significant indicators may include the absence or marked reduction of tonsils and cervical lymph nodes. For patients presenting with frequent otitis media and/or sinusitis, the assessment of serum immunoglobulin (Ig) concentrations is warranted if tonsils and cervical lymph nodes are notably small or absent.Further evaluations should involve

Table 1. Primary immunodeficiencies that frequently cause otitis media

Disease Name	Subtype	Pathophysiology	Age of Diagnosis	Primary ENT Findings and Infections	Potential Pathogens	Treatment
1. X-linked (Bruton's) Agammaglobulinemia (XLA)	Humoral Immunodeficiency	Mutation in Bruton's tyrosine kinase (Btk) leading to impaired B cell differentiation	After 6 months	Absence or significant reduction of tonsils, absence of cervical lymph nodes, recurrent pyogenic upper respiratory tract infections	*Pseudomonas aeruginosa*, *H. influenzae*, pneumococcus, and other streptococci	IVIG therapy, Antibiotic therapy
2. Common Variable Immunodeficiency (CVID)	Humoral Immunodeficiency	Low serum immunoglobulin concentration, defective specific antibody production, possibly polygenic	Variable based on symptom severity (diagnosis can occur in adulthood)	Chronic respiratory infections, sinusitis, otitis media, intestinal system infections	Encapsulated bacteria, Herpesvirus family	IVIG therapy and Antibiotic prophylaxis
3. IgG Subclass Deficiency	Humoral Immunodeficiency	Not clearly defined; may involve B cell differentiation disorders	Typically in childhood	Recurrent ear infections, sinusitis, bronchitis, and pneumonia	Particularly encapsulated bacteria	IVIG therapy, Antibiotic therapy
4. Selective IgA Deficiency (IgAD)	Humoral Immunodeficiency	Not clearly defined; potentially defects in class switching	After age 4	Rhinosinusitis, otitis media, mastoiditis, adenotonsillitis, and recurrent parotitis	*Streptococcus pneumoniae*, *Haemophilus influenzae* (encapsulated bacteria)	Antibiotic therapy during infections or prophylactically; IgA replacement is not recommended due to anaphylaxis risk
5. Hyper-IgM Syndrome (HIGMS)	Humoral Immunodeficiency	CD40 Ligand defect leading to IgM production due to impaired B cell differentiation	6 months - 2 years	Peritonsillar and other soft tissue infections, adenotonsillar hypertrophy, pneumonia	*Pneumocystis carinii* pneumonia	IVIG therapy, Antibiotic therapy, G-CSF if necessary
6. Wiskott-Aldrich Syndrome	Combined Immunodeficiency	Mutations in WASP (Wiskott-Aldrich Syndrome Protein)	Within the first year	Pneumonia, sepsis, meningitis, otitis media	Encapsulated bacteria, *P. carinii*, Herpesvirus	IVIG, splenectomy, Bone marrow transplantation

measuring the percentage of peripheral circulating B cells if at least two of the three primary serum Ig classes (IgM, IgG, and IgA) are below normal levels (11).

Clinical outcomes are generally favorable with gammaglobulin replacement therapy and aggressive antibiotic use. Boys with XLA experience improved quality of life with appropriate treatment, and life-threatening infections are rare among those receiving intravenous gammaglobulin (12).

Common Variable Immunodeficiency (CVID)

Common Variable Immunodeficiency is characterized by low serum immunoglobulin levels, defective specific antibody production, and increased susceptibility to bacterial infections. Patients with CVID often present with autoimmune cytopenias, lymphoproliferative disorders, and granulomas, coupled with frequent respiratory tract infections. Accumulated mucus in the airways may lead to obstruction, bacterial colonization, and recurrent infections. Due to anatomical factors, the middle ear and upper respiratory tract are particularly affected in children (13).

The most common infections in CVID include acute bronchitis, pneumonia, acute otitis media, chronic bronchitis, and chronic sinusitis. Diagnosis is often delayed, typically occurring 5.8 to 8.9 years after symptom onset. The high incidence of recurrent minor infections and significant overlap with atopic conditions complicates the diagnostic process (14,15).

Literature reports on otitis media prevalence in CVID patients vary between 25% and 98% (15–19). Advances in diagnostic and therapeutic approaches, including timely intravenous immunoglobulin (IVIG) treatment, have significantly reduced CVID-related mortality. B cell abnormalities continue to play a critical role in the chronic disease trajectory and prognosis (20–22).

IgG Subclass Deficiency

The four IgG subclasses (IgG1, IgG2, IgG3, and IgG4) account for approximately 70%, 20%, 7%, and 3% of total IgG levels, respectively. Each subclass has unique structural, antigenic, and biological properties. Notably, IgG2 is crucial for antibody responses against polysaccharide antigens. IgG subclass deficiency is defined by normal or near-normal total IgG levels but with one or more subclasses below age-appropriate norms by less than 2 standard deviations (23).

Clinically, both children and adults with IgG subclass deficiency often experience recurrent respiratory infections, including otitis media, sinusitis, and bronchitis, due to common respiratory pathogens. In children under ten, a deficiency in a single subclass may resolve spontaneously if there is no complete absence of the subclass. Symptomatic adults may progress to Common Variable Immunodeficiency (CVID). Regular subclass assessments are recommended for both children and adults (23).

Selective IgA Deficiency (IgAD)

IgA plays a critical role in mucosal immunity in the gastrointestinal and respiratory systems (24). The pathophysiology of selective IgA deficiency is not entirely understood but may involve impaired differentiation of B lymphocytes into IgA-secreting plasma cells and defective class switching (25). Diagnosis is confirmed in individuals aged 4 years and older when serum IgA levels are less than 0.07 g/L (26). This deficiency, which can range from partial to complete absence, impairs mucosal immunological barriers and increases susceptibility to infections, autoimmunity, and allergies (24).

Most patients with IgA deficiency are asymptomatic; however, approximately one-third may experience recurrent infections, including frequent sinopulmonary and gastrointestinal infections. Heterologous IgA treatment poses risks of anaphylaxis in many patients due to anti-IgA antibodies (27).

Hyper-IgM Syndrome (HIgM)

Patients with Hyper-IgM syndrome typically exhibit normal or elevated levels of IgM. Recurrent bacterial sinopulmonary infections generally begin after the sixth month of life due to the protective effect of maternal immunoglobulins. In children under two years, recurrent otitis media, respiratory infections, and Pneumocystis carinii pneumonia are commonly observed.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich Syndrome, inherited in an X-linked recessive pattern due to mutations in the Wiskott-Aldrich Syndrome Protein (WASP), is characterized by impaired cellular immunity and reduced antibody responses to polysaccharide and protein antigens (IgM and sometimes IgG) (28).

Infections such as pneumonia, sepsis, meningitis, and otitis media often occur within the first year of life, primarily caused by pneumococci, encapsulated bacteria, P. carinii, and herpesviruses. AOM, atopic asthma, and eczema are frequent in these patients. Survivors beyond infancy are at risk for autoimmune vasculitis and malignancy (29,30). Bone marrow transplantation can be considered if a matched sibling donor is available; otherwise, mortality rates are high in the second decade of life (31).

Secondary Immunodeficiencies

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)

Upper respiratory tract infections are common in HIV-infected individuals, occurring in about 40% of patients. Children with HIV frequently experience recurrent AOM, with pathogens including *Staphylococcus epidermidis*, *Pneumococcus*, *Enterococcus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Treatment typically involves broad-spectrum antibiotics, and surgical interventions, such as mastoidectomy, may be necessary in cases where medical management is inadequate. HIV patients face an elevated risk of unilateral and bilateral facial nerve paralysis (32).

Other causes of secondary immunodeficiency include chemotherapy, autoimmune diseases, malignancies, nephrotic syndrome, splenectomy, long-term corticosteroid use, and diabetes mellitus.

Management of Acute Otitis Media in Children with Immunodeficiency

In managing AOM in children with known immunodeficiencies, treatment should be tailored according to the specific type of underlying immunodeficiency. Antibiotic therapy should target possible etiological agents, and complications are more prevalent in these patients, necessitating more aggressive antibiotic treatment. Miringotomy can assist in identifying infecting organisms and determining their antibiotic sensitivities, guiding effective treatment choices. Early initiation of antibiotic therapy, and in some cases, parenteral treatment with intravenous antibiotics, can help control the disease. Treatment should involve collaboration between infectious disease specialists and otolaryngologists, with preparedness for potential complications.

For children with immunodeficiency who frequently develop ear infections, long-term prophylactic antibiotics may reduce the frequency of AOM episodes by up to 50% (33). Continuous or intermittent antibiotics are used in various immunodeficiencies associated with frequent otitis media, such as Wiskott-Aldrich Syndrome, Common Variable Immunodeficiency, specific antibody deficiency, IgA deficiency, chronic

granulomatous disease, and C2 deficiency (34,35). While prophylactic antibiotics do not replace immunoglobulin and antibody replacement therapy, they are commonly used in immunodeficient patients despite limited clinical research on their efficacy. For patients with recurrent and complicated infections despite the use of prophylactic antibiotics, and those with hypogammaglobulinemia, immunoglobulin replacement therapy should be prioritized (36).

In secondary immunodeficiencies, addressing the underlying condition is essential, and treatment should be tailored accordingly.

Conclusions

Otitis media is one of the most prevalent conditions in childhood, with its frequency and severity influenced by developmental and environmental factors. Recurrent otitis media is commonly encountered in clinical practice and can present significant treatment challenges. Although immunodeficiencies are rare, they can be overlooked in intensive clinical settings, leading to issues with disease progression, complication development, and increased treatment costs. Aggressive treatment of immunodeficiencies and a multidisciplinary approach are crucial for effective management.

Conflict of interest statement

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