

Otitis Media in Children with Congenital Immunodeficiencies

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Abstract Otitis media represents one of the most common infections in childhood. Within the first 3 years of life, up to 80% of children experience at least one episode of otitis media. It is often resolved with supportive therapies and consequently not considered a worrisome problem. However, it may be an early manifestation of a severe underlying disease. Primary immunodeficiencies are rare congenital defects of the immune system that often remain unrecognized, or diagnosis can be delayed, sometimes resulting in fatal consequences for the child. Patients suffer from recurrent, prolonged, and/or unusual infections leading to local sequelae, failure to thrive, developmental delays, and systemic infections with severe courses. This review provides a brief insight into primary immunodeficiencies and an overview of leading findings that should result in further evaluation of the immune system in cases of otitis media. A stepwise diagnostic approach is proposed to facilitate early and accurate diagnosis and, consequently, effective and timely therapy to improve the patient's outcome and quality of life.

Keywords Otitis media · Recurrent infections · Diagnostic approach · Primary immunodeficiency · Immunoglobulin · Neutropenia · Common variable immunodeficiency (CVID) · Severe combined immunodeficiency (SCID) · Hypogammaglobulinemia · Chronic granulomatous disease (CGD)

Introduction

Otitis media is one of the most common infections in childhood. Within the first 3 years of life, up to 80% of children will have experienced at least one episode of otitis media requiring specific treatment [1]. Otitis media is a leading reason for children to be seen by a pediatrician, which leads to marked expenses of the health care system [2], especially when underlying disorders remain unrecognized. The burden of infectious disease is immense even in children with a perfectly healthy immune system, as a frequency of up to 12 episodes of infection per year is considered within the normal range for children younger than 6 years of age [3]. This high frequency of infections is partially a result of the immature immune system being exposed to a variety of pathogens for the first time, and often causes distress for patients and their families. Because it represents such a common finding, it is difficult, but nevertheless of major importance, to remain aware that otitis media can be symptom of an underlying immunologic disorder requiring further diagnostic evaluation.

In early childhood, upper airway infections rarely occur without effusion in the middle ear, often associated with an earache and thus putting the child in serious distress, mainly during the night. In general, adequate analgesia and consequent use of local swell-reducing medication prevent the development of a bacterial superinfection and relieve the pain. Despite lack of evidence, preemptive antibiotic therapy is commonly prescribed [4•].

Why is otitis media, or middle ear effusion, so common following common viral infections in this age group? First, the anatomy of the eustachian tube is different, with a smaller angle of the orifice to the nasopharyngeal space. At this location, extensive lymphoid tissue is growing disproportionately compared with the surrounding tissue due to the development of the adaptive immune system. The

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consequence is obstruction of the choanae, which leads to chronically impaired nasal respiration and recurrent local infections enhancing the swelling of the surrounding mucus membranes. The obstructed inflow of air into the eustachian tube may result in resorption of the air in the middle ear and reactive effusions. Besides providing a fertile ground for recurrent bacterial infection, this is a frequent cause of impaired hearing and speech development in children [4••]. Chronic recurrent episodes in an otherwise-healthy child often can be solved by surgical removal of the adenoid hyperplasias, usually combined with a paracentesis of the eardrum and, occasionally, insertion of a pressure-equalizing tube. However, this surgical approach lacks evidence of long-term benefit, according to a recent Cochrane review [5••].

So how can we know when further evaluation of the child is necessary? Warning signs include progressing infections leading to mastoiditis; associated abscesses or systemic infections; lack of responsiveness to adequate antibiotic treatment; or occurrence of unusual, severe, or frequently relapsing infections in other sites. If recurrent otitis media is associated with failure to thrive and general developmental delay, an underlying disease such as a primary immunodeficiency needs to be ruled out. Accompanying symptoms are path leading (Table 1). Children with antibody deficiencies have a history of upper and lower respiratory tract infections, frequently including sinusitis. In defects of the leukocytic and phagocytic system, abscesses represent pathognomonic symptoms. Severe combined immunodeficiencies (SCIDs) and HIV infection typically present with opportunistic infections, chronic diarrhea with failure to thrive, and infections with intracellular pathogens. Therefore, the nature of pathogens causing the ear infection also provides relevant diagnostic information; for example, a predominance of capsulated bacteria is associated with selective IgG subclass 2 deficiency. Some immunodeficiency syndromes include additional risk factors, such as anatomic malformations of the nasopharynx in DiGeorge syndrome. In the following, we present a brief overview of the immunodeficiencies involving otitis media as the accompanying or presenting manifestation, with emphasis on the landmarks that should raise suspicion in the consulted general practitioner; pediatrician; or ear, nose, and throat specialist and lead to further evaluation of the child's immune system.

Defects of the Adaptive Immune System

Antibody Deficiency Syndromes

Selective IgA Deficiency

The leading diagnostic features are low or absent IgA in plasma and on mucus membranes.

Selective deficiency of IgA, with a frequency of 1 in 600, is very common and often found incidentally during screening of clinically healthy blood donors [6]. However, it has been associated with a higher incidence of infections of the upper respiratory tract, as well as otitis media [7]. IgA deficiency is found in up to 20% of patients with gluten-sensitive enteropathy and may lead to misinterpretation of some diagnostic tests [8]. The detection of serum IgA deficiency in patients with recurrent or chronic otitis should always lead to further diagnostic evaluation of the immune system, including potentially associated IgG subclass deficiency [9], as it may not solely explain the problem. Replacement therapy comparable to intravenous IgG (IVIG) is not available or indicated for selective IgA deficiency and may lead to hypersensitivity reactions [10]. Antibiotic prophylaxis or surgical therapies may be required in the absence of treatable associated immune deficiencies.

Immunoglobulin Subclass Deficiencies

The leading diagnostic feature is low serum IgG subclass with normal total IgG.

Defects in the IgG subclasses occur singularly or in combination with IgA deficiency, with the latter representing a binding link between selective IgA deficiency and common variable immunodeficiencies (CVIDs) [9]. In particular, defects of the subclass IgG₂ require attention in the context of otitis media. This subclass is strongly involved in the humoral response to polysaccharides and hence to encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [11]. The delayed development of the T-independent immune response type 2 toward polysaccharides, which is hampered during the first 12 to 24 months of life, leads to a specific vulnerability to these organisms [12]. Levels of IgG₂ have been reported to be reduced in up to 33% of children with recurrent otitis media, and a complete lack of this subclass has been reported in 2.5% of children [13]. Due to the predominance of IgG₁ and the presence of two further subclasses, isolated IgG₂ deficiency may be present despite normal serum levels of total IgG. Therefore, the extended diagnostic approach in suspicion of immunodeficiency underlying recurrent otitis media should include IgG subclass quantification, especially considering that these children can be treated successfully with IVIG substitution [11, 14].

Common Variable Immunodeficiencies

The leading diagnostic features are reduced IgG and IgM and/or IgA, and impaired vaccine response.

CVIDs represent a melting pot of various—mostly unknown—entities characterized by identical clinical and immunologic findings: reduction of the serum levels of IgG

Table 1 Congenital immunodeficiencies associated with otitis media

Associated symptoms	Possible disorders	Typical pathogens	Basic diagnostic tests	Advanced diagnostic tests	Therapeutic options
Recurrent upper airway infections; history of sepsis; pneumonia; mastoiditis; complicated local infections, often with encapsulated bacteria; in CVID additionally autoimmune symptoms (eg, thrombocytopenia, vitiligo) and/or allergy-like symptoms	Immune globulin deficiency syndromes: IgA deficiency, IgG subclass deficiency; toddler age: XLA, CVID	<i>Streptococcus pneumoniae</i> ; <i>Haemophilus influenzae</i> ; <i>Neisseria meningitidis</i> ; <i>Staphylococcus aureus</i>	White blood cell count and differentiation; serum protein; CRP; IgG, IgM, IgA, IgE	Lymphocyte subpopulations (T and B lymphocytes); lymphocyte stimulation tests; IgG subclasses 1–4; vaccine response; genetic and disease-specific testing (eg, BTK, CD40/CD40 ligand, ICOS, TACI)	IgG substitution (IVIG); antibiotic prophylaxis; surgery (eg, PE tubes, adenoidectomy)
Opportunistic infections or atypical pathogens; failure to thrive; chronic diarrhea; rash; life-threatening infections	Severe combined immunodeficiency; metabolic disorders of the lymphocytes (eg, ADA or PNP deficiency); hyper-IgM syndrome	<i>Pneumocystis jiroveci</i> ; cytomegalovirus; fungi; atypical mycobacteria; all bacteria	White blood cell count and differentiation; lymphocyte subpopulations (T and B lymphocytes); serum protein; CRP; IgG, IgM, IgA, IgE	Lymphocyte stimulation tests; genetic and disease-specific testing (eg, common γ -chain, Artemis, JAK, STAT, CD40/CD40 ligand, ADA, PNP)	HSCTx
Cleft palate; micrognathia; low-set ears; cardiac malformations (especially including the aortic arch); hypocalcemia; developmental delay	Microdeletion 22q11 syndromes (DiGeorge, Shprintzen, velocardiofacial)	All bacterial/opportunistic infections possible	White blood cell count and differentiation; lymphocyte subpopulations (T and B lymphocytes); echocardiography; chest x-ray	FISH testing for microdeletion 22q11 syndromes	Thymus transplantation; IVIG; sometimes HSCTx; antibiotic prophylaxis; surgery (eg, PE tubes, adenoidectomy)
Microcephaly; neoplasms; skin anomalies; progressive ataxia; telangiectasia of the skin and eyes	Chromosomal breakage syndromes: Nijmegen breakage syndrome; ataxia-telangiectasia (Louis-Bar's syndrome)	All bacterial/opportunistic infections possible	White blood cell count and differentiation; serum protein; CRP; IgG, IgM, IgA, IgE	Chromosomal stability testing	HSCTx for Nijmegen breakage syndrome; chemotherapy for neoplasms is risky due to frequent secondary tumors; neurological symptoms in ataxia-telangiectasia prodromal
Eczema; thrombocytopenia; small platelets	Wiskott-Aldrich syndrome	<i>S. aureus</i> ; variable bacteria and fungi; viral infections	Platelet count and volume; white blood cell count and differentiation; lymphocyte subpopulations (T and B lymphocytes); serum protein; CRP; IgG, IgM, IgA, IgE	Genetic and disease-specific testing (eg, Wiskott-Aldrich syndrome protein)	HSCTx in time; antibiotic prophylaxis; eczema treatment; surgery (eg, PE tubes, adenoidectomy)
Coarse face; eczema; allergic symptoms; tooth abnormalities	Hyper-IgE syndrome	<i>S. aureus</i> ; <i>Candida</i> spp; <i>S. pneumoniae</i> ; variable bacteria and fungi	White blood cell count and differentiation; serum protein; CRP; IgG, IgM, IgA, IgE	Genetic and disease-specific testing: STAT3, TYK8, DOCK8	HSCTx in time; antibiotic prophylaxis; eczema treatment; surgery (eg, PE tubes, adenoidectomy)
Abscesses of skin and lymph nodes; dental abscesses; cellulitis without pus formation; empyema; candidiasis; delayed detachment of umbilical cord	Granulocytic deficiencies: chronic granulomatous disease, cyclic neutropenia, Kostmann's syndrome, leukocyte adhesion disorders	<i>S. aureus</i> ; <i>Candida</i> spp; <i>Aspergillus</i> spp; variable bacteria	White blood cell count and differentiation; serum protein; CRP; for DD: IgG, IgM, IgA, IgE	Dihydrorhodamine test; bone marrow aspirate; genetic and disease-specific testing (eg, CD18, adhesion molecules)	Granulocyte-stimulating factor in disorders with low numbers; HSCTx for functional defects; antibiotic prophylaxis and surgeries

Typical associated symptoms and pathogens may be path leading. This overview is limited to the most frequent immunodeficiencies; many other defects should be considered in individual cases. Consultation with a specialized center for pediatric immunology should occur early to rationalize and direct the diagnostic and therapeutic approach

ADA adenosine deaminase; BTK Bruton tyrosine kinase; CRP C-reactive protein; CVID common variable immunodeficiency; DD differential diagnosis; DOCK Rho-Rac guanine exchange factors; FISH fluorescence in situ hybridization; HSCTx hematopoietic stem cell transplantation; ICOS inducible co-stimulator; IVIG intravenous immunoglobulin; JAK janus kinase; PE pressure-equalizing; PNP purine nucleoside phosphorylase; STAT signal transducer and activator of transcription; TACI transmembrane activator and calcium modulator and cyclophilin ligand interactor; TYK nonreceptor protein tyrosine kinase; XLA X-linked agammaglobulinemia

and at least one additional immunoglobulin class (IgM and/or IgA), recurrent infections, and impaired specific antibody responses to vaccinations [15]. In a minority of CVID patients, genetic defects (eg, of the inducible co-stimulator in the B-cell coreceptor component CD19 or the receptors for the B-cell-activating factor) have been found to be causative [15]. Many cases occur sporadically; however, analysis of the clinical and immunologic situation of close relatives frequently reveals similar symptoms, as well as minor antibody deficiencies, selective IgA deficiency, IgG subclass deficiencies, or sometimes even unrecognized CVID [16•, 17].

Otitis media is very common in these children and young adults and is not uncommonly the presenting complaint [18]. In an analysis of our pediatric CVID patients, we found 69% with relapsing (three or more episodes per year) or chronic otitis [16•]. Similar prevalence has been noted in the largest reported cohort [18] and in registries [19]. Mastoiditis occurred in 10% of the children with primary CVID, a remarkably high rate, illustrating the risk of *per continuitatem* spread of the infection due to lack of surface immunity. In contrast to patients with agammaglobulinemia, B cells are present in these children. Therefore, secondary lymphatic tissue is also present, which is frequently hypertrophic, supporting the development of middle ear infection by the above-mentioned mechanical obstruction.

Accompanying findings raising suspicion for CVID are recurrent bacterial infections of the respiratory tract (present in nearly all patients), as well as allergy-like symptoms and autoimmune diseases (predominantly autoimmune hemolytic anemia or thrombocytopenia, vitiligo, and granulomatosis), both of which are found in about 30% to 50% of the patients [15, 16•]. A first screening to exclude the diagnosis or enforce further investigation is the quantification of the serum levels of IgG, IgA, and IgM. Regular, individual-based, dose-adapted treatment with IVIG should improve the rate and severity of ear infections. However, as in some patients, the entity includes T-cell function impairment, otitis symptoms may persist and require prolonged treatment with antibiotics and drainage of the middle ear.

X-linked and Autosomal Agammaglobulinemia

The leading diagnostic features are low or absent circulating B lymphocytes and immunoglobulin levels.

X-linked agammaglobulinemia is caused by a defect of the Bruton tyrosine kinase (BTK) [20]. Without BTK, rearrangement of the immunoglobulin genes is severely impaired, and a maturation stop at the pro-B-cell level occurs in nearly all B cells, resulting in markedly reduced numbers of mature circulating B cells, low immunoglobulin levels, and absence of organized lymph nodes [21].

Recurrent or chronic otitis media is very common in affected boys (X-linked recessive inheritance) and is often part of the initial complaints. Inappropriately small tonsils and the absence of enlarged lymph nodes despite recurrent airway infections are the striking findings that should raise suspicion of agammaglobulinemia. Severely reduced levels of IgM can already be found in infants, while the defective production of IgG remains invisible in the first months of life due to prenatally transmitted maternal antibodies. This maternal protection also explains why the usual onset does not occur prior to early toddler age [20]. The lack of humoral immune responses, including the deficiency to produce and secrete IgA to the surface of mucus membranes, predisposes these patients to bacterial infections of the upper airways. Recurrent acute otitis media is present in the vast majority of X-linked agammaglobulinemia patients [22]. Chronic and complicated courses of otitis requiring middle ear or mastoid surgeries are among the main long-term problems of these children [22]. A history of invasive infection or bacterial sepsis, especially with encapsulated bacteria such as *H. influenzae* or *S. pneumoniae*, should raise suspicion and lead to specific diagnostic testings.

The white blood and lymphocyte count is mostly normal, whereas a finding of less than 2% mature B cells is typical. Confirmation of the diagnosis occurs via genetic analysis or proof of absent BTK in flow cytometric analysis of macrophages or platelets. In girls with similar findings or suspicious boys with normal BTK, autosomal recessive agammaglobulinemia is possible [23].

In agammaglobulinemia, consequent substitution therapy with adequate doses of IVIG improves or relieves the occurrence of infections, including otitis media [24, 25]. In prolonged courses of otitis media that cannot be resolved with IVIG and antibiotics, invasive procedures such as drainage may be necessary.

Severe Combined Immunodeficiencies

The leading diagnostic features are absent, reduced, or functionally deficient lymphocytes and reduced immunoglobulin levels.

A variety of immunodeficiencies impact both T- and B-cell function and various other components of the adaptive immune system. As CD4⁺ T cells functionally coordinate the adaptive immune response, their absence or lack of functioning results in severe dysfunction of antigen-specific immune responses. In the most frequent variant, X-linked SCID, a defect in the common γ -chain leads to absence of T and natural killer cells in the presence of normal numbers of nonfunctional B cells, which can lead to normal total lymphocyte counts despite the lymphocytes being functionally incapable of mounting a protective immune response [26]. In recent years, various genetic defects, mainly involving

proteins participating in signal transduction cytokine production or *VDJ* rearrangement, have been identified as causes of inherited SCID with various combinations of absent or reduced lymphocyte populations, such as T cells, B cells, or natural killer cells, as well as the presence of nonfunctional lymphocytes [27]. In some metabolic disorders (eg, adenosine deaminase deficiency), lymphocytes accumulate toxic products and lack the capability to proliferate when activated by an antigen, and subsequently undergo apoptosis. The hyper-IgM syndrome is caused by a lack of CD40 or its ligand (CD40L) and is characterized in most patients by high levels of IgM and low or absent IgG due to the incapability for maturation switch of activated IgM-expressing B cells to IgG expression/production. As the communication deficiency also impairs antigen presentation, the clinical manifestation of the hyper-IgM syndrome is similar to that of a SCID and thus should be part of the diagnostic work-up in suspected children.

Most of these syndromes may present with the clinical features discussed previously for immunoglobulin deficiencies, including recurrent otitis media. However, due to the severely impaired immune response, these children likely will develop fulminant systemic infections (sometimes originating from otitis) or life-threatening opportunistic infections rather than presenting with chronic local infection, such as otitis.

For many of these deficiencies, hematopoietic stem cell transplantation (HSCTx) is the only curative therapy [28•]. Successful gene therapies remain limited to small series of specific cases [29]. After HSCTx, children often remain in a state of impaired immunity, sometimes for years, due to incomplete immune reconstitution or immunosuppression in response to graft-versus-host disease [30]. Therefore, preexisting problems with recurrent otitis media may persist and require IVIG substitution, antibiotic prophylaxis, or surgical treatment.

Microdeletion 22q11 Syndromes

The leading diagnostic features are absent mature T lymphocytes and associated malformations of variable extent.

Microdeletion 22q11 syndromes include different extensions of a complex of deficiencies in organogenesis that is derived from impaired embryologic development of the third and fourth pharyngeal pouch. The complete syndrome is described as DiGeorge, Shprintzen, or velocardiofacial syndrome. Besides the presence of cleft palate and facial stigmata as retrognathia and low-set ears, the syndrome presents as absence of the parathyroid glands and the thymus, as well as cardiac malformations and developmental delay [31]. Although otitis media is usually not the leading symptom in the complete syndrome, it represents one of the major health issues facing affected patients. This

is obvious considering the combination of absent thymus, resulting in a lack of naive T cells, and the anatomic malformations hampering pneumatization of the middle ear due to the pharyngeal anatomic defects. Most children with this syndrome require pressure-equalizing tubes to achieve sufficient freedom from recurrent otitis media and to ensure normal hearing and speech development. Recognition of the common entity of immunodeficiency and cleft, and the severity of potential complications (eg, hypocalcemia) should lead to basic immunologic diagnostics and genetic screening in patients with cleft palate. Since fluorescence in situ hybridization has become diagnostic, standard microdeletions in the q11 region of chromosome 22 were observed in many children with only one or a few of the symptoms associated with this complex [32]. In cases involving total absence of the thymus, heterotopic transplantation of thymic stroma has been performed successfully [33].

Wiskott-Aldrich Syndrome

The leading diagnostic features are thrombocytopenia, eczema, and reduced antibodies to *S. pneumoniae*.

Wiskott-Aldrich syndrome (WAS) is clinically characterized by the triad of thrombocytopenia, eczema, and frequent infections. It is caused by a recessively inherited deficiency of the gene coding for the WAS protein located on the X chromosome [34]. The complete syndrome therefore is found nearly exclusively in boys, while female carriers may express minor or subclinical symptoms. Lack or nonfunction of the WAS protein hampers rearrangements of the cytoskeleton, reducing the capability of lymphocytes to migrate and interact. T-cell deficiency leads to the risk of developing opportunistic infections such as *Pneumocystis jiroveci* pneumonia. Furthermore, development of specific antibody responses is impaired, especially toward encapsulated bacteria such as *S. pneumoniae*, *Neisseria meningitidis*, and *H. influenzae*, which represent the main pool of pathogens causing otitis media [35]. Therefore, otitis media is a very common finding in these children, as are sepsis, meningitis, and pneumonia. Although supportive therapies, including chemoprophylaxis against bacterial and viral infections, and IVIG help stabilize the clinical problems of the patients and reduce the frequency of infections, the only promising curative treatment is HSCTx. This therapy often improves the eczema as well; however, it leaves some patients in a state of imperfect immunity and necessitates post-transplant therapies, as mentioned previously for other children, following HSCTx [36].

Granulocyte Deficiencies

The leading diagnostic feature is granulocyte deficiency in number or function.

Granulocytes form one of the main components of the innate immune system. They are not reactive toward specific antigens following previous contact but instead rely on a variety of mechanisms to recognize nonself or dedifferentiated structures, including opsonization by antibodies or complement fragments, or absence of Toll-like receptors [37••]. Besides the secretion of antimicrobial substances and the generation of fibrinoid nets, so-called neutrophil extracellular traps [38], the main participation of neutrophil granulocytes in the host defense happens by phagocytosis of infiltrating organisms, which are then destroyed by hydrolytic enzymes and reactive oxygen species within phagosomes [39].

Granulocytes therefore form a nonadaptive immune function that is present at birth. Hence, the symptoms of their absence or dysfunction usually develop early in life, with a delayed release of the umbilical cord residuum as a typical, but not often consciously noted symptom.

A common cause of neutropenia at a young age is the presence of antineutrophil antibodies of alloimmune (transplacental maternal) or autoimmune origin [40]. Inherited disorders leading to reduced numbers of neutrophils are severe congenital neutropenia (Kostmann's syndrome) and cyclic neutropenia [41], as well as Shwachman syndrome with associated exocrine pancreas deficiency [42]. Furthermore, neutropenia can be part of bone marrow suppression caused by, for example, toxins, radiation, infections, or neoplasms.

Other disorders show normal or elevated numbers of granulocytes but functional deficiencies. These include deficits in adhesion to endothelial cells, preventing migration into tissues (leukocyte adhesion deficit 1–3), phagocytosis, or the capability to generate reactive oxygen species and therefore to kill and degenerate the phagocytosed pathogens or fragments (chronic granulomatous disease [CGD]). CGD is characterized by the formation of granulomas, circular arrangements of activated macrophages, and lymphocytes, representing an effort to encapsulate and control the infiltrating pathogens [43].

The lead clinical symptom of granulocytic disorders is the formation of abscesses of skin and lymph nodes, pneumonia, and empyema, accompanied by the formation of granulomas in cases of CGD [44]. Several studies have described recurrent otitis media as one of the most frequent clinical findings in neutropenic disorders such as autoimmune neutropenia [40] or various genetic neutropenias [45]. In CGD, otitis media was not described as a leading symptom, but obstructing granulomas sometimes led to secondary otitis media and sequelae [46]. Infections in patients with granulocytic deficiencies are often caused by *Staphylococcus aureus*; however, the most threatening and harmful are fungal infections, especially with *Aspergillus* and *Candida* spp [44].

A white blood count is a basic diagnostic test that often reveals the lack of granulocytes but needs to be followed by specific tests to determine the origin of the absence, such as antibody screening and often bone marrow aspiration and genetic testing. If cyclic neutropenia is suspected, repeated measurements need to be performed every third day over the course of several weeks. Functional tests of the granulocytes in cases of normal quantitative presence are only available in specified laboratories and should be requested in collaboration with a pediatric immunologist. The generation of reactive oxygen species can be detected by the dihydrorhodamine test, while other deficits require leukocyte chemotaxis testing [47]. Genetic testing often may be required.

In disorders with low numbers of granulocytes, therapy with granulocyte colony-stimulating factor increases the presence of usually functional circulating granulocytes. Higher frequency of myeloid leukemia has been associated with long-term granulocyte colony-stimulating factor therapy [48]; therefore, monitoring for mutations within the granulocytes is recommended. HSCTx is an option as a curative approach, but the optimal timing for this hazardous treatment is difficult to determine, especially if no HLA-matched sibling is available as a potential lower-risk donor [49]. Although it seems difficult to justify such an invasive procedure as long as alternative options are available to maintain patients in a clinically stable condition, good clinical condition improves the chances of success and post-transplant outcome. For severe functional deficits of the granulocytes, HSCTx remains the only promising long-term therapy [49].

In all granulocytic disorders, subsequent antibiotic therapy for otitis media and other infections is required, and drugs with intracellular effects such as ofloxacin, ciprofloxacin, or cotrimoxazole should be part of the regimen. For nonresponsive infections, fungal agents must be considered. Early and profound antibiotic treatment of otitis media is required to avoid *per continuitatem* extension of the infection and severe sequelae. Antifungal prophylaxis, including avoidance of *Aspergillus* spp exposure via face mask protection, is part of routine treatment [44].

Rarer Inborn Disorders of the Immune System

Almost every component of the immune system can be quantitatively or functionally deficient. Many defects have been described in case reports or smaller case series. Defects of the complement system are mainly associated with infections with capsulated bacteria and, therefore, with otitis media. The threat within these disorders is the danger of overwhelming systemic infections originating from a “trivial” local infection such as otitis media [50]. A similar situation is present in defects of the signaling pathway of

the nuclear factor “ κ light-chain enhancer” of activated B cells (NF κ B), with vulnerability toward capsulated bacteria, while screening immune tests show normal results [51]. Ataxia-telangiectasia (Louis-Bar’s syndrome) and Nijmegen breakage syndrome are associated with impaired repair of breaks in the DNA double-strand. Consequently, the combined immune deficiency is accompanied by increased risk of developing neoplasms. In ataxia-telangiectasia, patients develop progressive cerebellar dysfunction leading to disabling ataxia and several skin abnormalities, such as telangiectasia and vitiligo, while children with Nijmegen breakage syndrome are microcephalic and show developmental delay [52]. Due to the risk of additional DNA breakage, x-ray diagnostics should remain limited to the necessary minimum, and HSCTx as a therapeutic option is a challenge. The hyper-IgE syndrome is characterized by severe eczema and facial feature and tooth abnormalities and is frequently associated with otitis media and externa. The immunodeficiency has been associated with several defects in genes coding for signal-transducing enzymes [53].

Otitis media and recurrent infections are also part of many metabolic disorders, including common diseases such as diabetes mellitus or chromosomal aberrations such as Down syndrome. Many children with other health conditions require treatment that impairs the immune system purposely (eg, immunosuppressive agents for transplantation or autoimmune disorders) or as an adverse effect. Therefore, the consultation of various specialists involved in patient care is essential.

Conclusions and Rational Diagnostic Approach

That otitis media is one of the most common infectious diseases in children should not lead to underestimation of its role as a first symptom of a severe underlying disorder. Most children with recurrent otitis media will not reveal a deficient immune system beyond the physiologic immaturity. However, congenital immunodeficiencies do exist, and it is not unlikely that unrecognized immunodeficiencies are the cause of some severe and potentially fatal infections.

A history of recurrent, unusual, or severe infections; chronic diarrhea; failure to thrive; or a family history of immunodeficiencies or fatal pediatric infections should raise awareness and lead to further investigation. Table 1 presents a brief overview of the most common and relevant congenital immunodeficiencies associated with otitis media. A profound documentation of the patient history and associated symptoms may be directive for a rational, stepwise diagnostic approach. Although some disorders can be discovered with routine screening tests such as white blood cell count or serum IgG levels, others require highly

specific and not routinely available tests and, therefore, expert advice. A specialized center should be included in the diagnostic approach as soon as the primary care physician suspects contribution of a deficient immunity to the otitis media problems. This way, early recognition of a disorder can occur without performing unnecessary, costly, and sometimes invasive diagnostic testing, and the optimal therapeutic approach can be initiated without delay.

This review provides only a limited insight into congenital immunodeficiencies and the rapidly increasing knowledge about them. The involvement of a pediatric immunology specialist is crucial, as even if the basic clinical work-up is completely normal, it still may be a primary immunodeficiency.

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References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Teele DW, Klein JO, Rosner B: Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J Infect Dis* 1989, 160:83–94.
2. Berman S, Byrns PJ, Bondy J, et al.: Otitis media-related antibiotic prescribing patterns, outcomes, and expenditures in a pediatric medicaid population. *Pediatrics* 1997, 100:585–592.
3. Rosenfeld RM, Culpepper L, Doyle KJ, et al.: Clinical practice guideline: otitis media with effusion. *Otolaryngol Head Neck Surg* 2004, 130:S95–S118.
4. •• Vergison A, Dagan R, Arguedas A, et al.: Otitis media and its consequences: beyond the earache. *Lancet Infect Dis* 2010, 10:195–203. *This was a consensus report of a working group of various specialists to optimize a diagnostic and therapeutic approach to otitis media.*
5. •• van den Aardweg MT, Schilder AG, Herkert E, et al.: Adenoidectomy for recurrent or chronic nasal symptoms in children. *Cochrane Database Syst Rev* 2010, 1:CD008282. *This Cochrane review highlighted the lack of controlled studies to prove the long-term benefit of surgical treatments for recurrent otitis media.*
6. Stiehm RE: The four most common pediatric immunodeficiencies. *Adv Exp Med Biol* 2007, 601:15–26.
7. Latiff AH, Kerr MA: The clinical significance of immunoglobulin A deficiency. *Ann Clin Biochem* 2007, 44:131–139.
8. Halfdanarson TR, Litzow MR, Murray JA: Hematologic manifestations of celiac disease. *Blood* 2007, 109:412–421.

9. Aghamohammadi A, Mohammadi J, Parvaneh N, et al.: Progression of selective IgA deficiency to common variable immunodeficiency. *Int Arch Allergy Immunol* 2008, 147:87–92.
10. Carbone J: Adverse reactions and pathogen safety of intravenous immunoglobulin. *Curr Drug Saf* 2007, 2:9–18.
11. Abrahamian F, Agrawal S, Gupta S: Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. *Clin Exp Immunol* 2010, 159:344–350.
12. Rijkers GT, Sanders EA, Breukels MA, Zegers BJ: Infant B cell responses to polysaccharide determinants. *Vaccine* 1998, 16:1396–1400.
13. Veenhoven R, Rijkers G, Schilder A, et al.: Immunoglobulins in otitis-prone children. *Pediatr Res* 2004, 55:159–162.
14. Abdou NI, Greenwell CA, Mehta R, et al.: Efficacy of intravenous gammaglobulin for immunoglobulin G subclass and/or antibody deficiency in adults. *Int Arch Allergy Immunol* 2009, 149:267–274.
15. Chapel H, Cunningham-Rundles C: Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. *Br J Haematol* 2009, 145:709–727.
16. •• Urschel S, Kayikci L, Wintergerst U, et al.: Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. *J Pediatr* 2009, 154:888–894. *This is the largest published pediatric CVID cohort. It describes specific clinical findings as well as childhood-specific long-term complications such as developmental delay and impaired growth.*
17. Aghamohammadi A, Sedighipour L, Saeed SE, et al.: Alterations in humoral immunity in relatives of patients with common variable immunodeficiency. *J Investig Allergol Clin Immunol* 2008, 18:266–271.
18. Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: clinical and immunological features in 248 patients. *Clin Immunol* 1999, 92:34–48.
19. Gathmann B, Grimbacher B, Beaute J, et al.: The European Internet-based patient and research database for primary immunodeficiencies: results 2006–2008. *Clin Exp Immunol* 2009, 157 (Suppl 1):3–11.
20. Ochs HD, Smith CI: X-linked agammaglobulinemia. A clinical and molecular analysis. *Medicine (Baltimore)* 1996, 75:287–299.
21. Maas A, Hendriks RW: Role of Bruton's tyrosine kinase in B cell development. *Dev Immunol* 2001, 8:171–181.
22. Moin M, Aghamohammadi A, Farhoudi A, et al.: X-linked agammaglobulinemia: a survey of 33 Iranian patients. *Immunol Invest* 2004, 33:81–93.
23. Lougaris V, Ferrari S, Cattalini M, et al.: Autosomal recessive agammaglobulinemia: novel insights from mutations in Ig-beta. *Curr Allergy Asthma Rep* 2008, 8:404–408.
24. Liese JG, Wintergerst U, Tympner KD, Belohradsky BH: High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child* 1992, 146:335–339.
25. Ochs HD, Gupta S, Kiessling P, et al.: Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol* 2006, 26:265–273.
26. Ochs HD, Notarangelo LD: X-linked immunodeficiencies. *Curr Allergy Asthma Rep* 2004, 4:339–348.
27. Notarangelo LD: Primary immunodeficiencies. *J Allergy Clin Immunol* 2010, 125:S182–S194.
28. •• Szabolcs P, Cavazzana-Calvo M, Fischer A, Veys P: Bone marrow transplantation for primary immunodeficiency diseases. *Pediatr Clin North Am* 2010, 57:207–237. *This is an overview about the indications, chances, and risks involved with HSCTx in primary immunodeficiencies.*
29. Santilli G, Thornhill SI, Kinnon C, Thrasher AJ: Gene therapy of inherited immunodeficiencies. *Expert Opin Biol Ther* 2008, 8:397–407.
30. Buckley RH: B-cell function in severe combined immunodeficiency after stem cell or gene therapy: a review. *J Allergy Clin Immunol* 2010, 125:790–797.
31. Sullivan KE: Chromosome 22q11.2 deletion syndrome: DiGeorge syndrome/velocardiofacial syndrome. *Immunol Allergy Clin North Am* 2008, 28:353–366.
32. Lindsay EA, Greenberg F, Shaffer LG, et al.: Submicroscopic deletions at 22q11.2: variability of the clinical picture and delineation of a commonly deleted region. *Am J Med Genet* 1995, 56:191–197.
33. Markert ML, Devlin BH, Alexieff MJ, et al.: Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. *Blood* 2007, 109:4539–4547.
34. Ochs HD, Notarangelo LD: Structure and function of the Wiskott-Aldrich syndrome protein. *Curr Opin Hematol* 2005, 12:284–291.
35. Notarangelo LD, Miao CH, Ochs HD: Wiskott-Aldrich syndrome. *Curr Opin Hematol* 2008, 15:30–36.
36. Pai SY, Notarangelo LD: Hematopoietic cell transplantation for Wiskott-Aldrich syndrome: advances in biology and future directions for treatment. *Immunol Allergy Clin North Am* 2010, 30:179–194.
37. •• Dale DC, Boxer L, Liles WC: The phagocytes: neutrophils and monocytes. *Blood* 2008, 112:935–945. *This is an accessible review about the current concept of the function of neutrophils and monocytes.*
38. Brinkmann V, Reichard U, Goosmann C, et al.: Neutrophil extracellular traps kill bacteria. *Science* 2004, 303:1532–1535.
39. Minakami R, Sumimoto H: Phagocytosis-coupled activation of the superoxide-producing phagocyte oxidase, a member of the NADPH oxidase (nox) family. *Int J Hematol* 2006, 84:193–198.
40. Bux J, Kissel K, Nowak K, et al.: Autoimmune neutropenia: clinical and laboratory studies in 143 patients. *Ann Hematol* 1991, 63:249–252.
41. Klein C, Welte K: Genetic insights into congenital neutropenia. *Clin Rev Allergy Immunol* 2010, 38:68–74.
42. Faber J, Lauener R, Wick F, et al.: Shwachman-Diamond syndrome: early bone marrow transplantation in a high risk patient and new clues to pathogenesis. *Eur J Pediatr* 1999, 158:995–1000.
43. Holland SM: Chronic granulomatous disease. *Clin Rev Allergy Immunol* 2010, 38:3–10.
44. Liese J, Kloos S, Jendrossek V, et al.: Long-term follow-up and outcome of 39 patients with chronic granulomatous disease. *J Pediatr* 2000, 137:687–693.
45. Rezaei N, Farhoudi A, Ramyar A, et al.: Congenital neutropenia and primary immunodeficiency disorders: a survey of 26 Iranian patients. *J Pediatr Hematol Oncol* 2005, 27:351–356.
46. Blayney AW, Bunch C: Mastoid surgery in chronic granulomatous disease. *J Laryngol Otol* 1984, 98:187–188.
47. Elloumi HZ, Holland SM: Diagnostic assays for chronic granulomatous disease and other neutrophil disorders. *Methods Mol Biol* 2007, 412:505–523.
48. Germeshausen M, Skokowa J, Ballmaier M, et al.: G-CSF receptor mutations in patients with congenital neutropenia. *Curr Opin Hematol* 2008, 15:332–337.
49. Elhasid R, Rowe JM: Hematopoietic stem cell transplantation in neutrophil disorders: severe congenital neutropenia, leukocyte adhesion deficiency and chronic granulomatous disease. *Clin Rev Allergy Immunol* 2010, 38:61–67.

50. Sjöholm A, Jonsson G, Braconier J, et al.: Complement deficiency and disease: an update. *Mol Immunol* 2006, 43:78–85.
51. Bustamante J, Boisson-Dupuis S, Jouanguy E, et al.: Novel primary immunodeficiencies revealed by the investigation of paediatric infectious diseases. *Curr Opin Immunol* 2008, 20:39–48.
52. Taylor AM, Groom A, Byrd PJ: Ataxia-telangiectasia-like disorder (ATLD)—its clinical presentation and molecular basis. *DNA Repair (Amst)* 2004, 3:1219–1225.
53. Freeman AF, Holland SM: Clinical manifestations, etiology, and pathogenesis of the hyper-IgE syndromes. *Pediatr Res* 2009, 65:32R–37R.