

Should Newborns be Screened for Immunodeficiency? Lessons Learned from Infants with Recurrent Otitis Media

Yesim Yilmaz-Demirdag

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Abstract Recurrent otitis media in children is considered one of the warning signs of primary immunodeficiencies (PIDs), particularly antibody deficiencies. Infants who have the most serious and potentially lethal form of PID, severe combined immunodeficiency (SCID), sometimes present with recurrent otitis media. Most of the time, because of the severity of the immune defect, they develop more serious and systemic infections. SCID is distinct among the PIDs and considered a pediatric emergency. Diagnosing SCID during the newborn period is crucial because survival completely depends on early diagnosis and treatment. Mortality declines significantly if immune reconstitution is established before 3.5 months of age, particularly before severe infections have occurred. However, most patients are diagnosed after they have suffered chronic or recurrent infections and developed permanent sequelae. Without institution of population-based newborn screening, most infants will miss the opportunity to live a healthy life.

Keywords Otitis media · Acute otitis media · AOM · Recurrent infections · Primary immunodeficiencies · Severe combined immunodeficiency · SCID · PID · T-cell excision circles · TRECs · Newborn screening · ADA deficiency · Antibody deficiency · Ataxia-telangiectasia · Upper respiratory tract infections · URI

Introduction

Recurrent otitis media is one of the most common reasons for referral to allergy and immunology clinics.

Y. Yilmaz-Demirdag (✉)
Department of Pediatrics,
West Virginia University School of Medicine,
One Stadium Drive,
Morgantown, WV 26506, USA
e-mail: ydemirdag@hsc.wvu.edu

Detailed history and careful physical examination as well as immunologic laboratory evaluation identify most of the patients with primary immunodeficiencies (PIDs). In our clinic, we have diagnosed a variety of PIDs in patients who have recurrent ear infections. One of the most interesting cases we have seen was diagnosed by just history and physical examination. The patient was a 6-year-old boy who was referred by his primary care physician for evaluation for recurrent respiratory tract infections. His past medical history was significant for mild cerebral palsy presenting as “clumsiness” that started at about 1 year of age, recurrent otitis media that resulted in hearing loss, and recurrent sinusitis and pneumonia in the past 1 year. Physical examination revealed a very pleasant young boy who appeared to be small for his age. He had conjunctival telangiectasia, erythematous scaly dermatitis on the arms and legs (Fig. 1) and truncal ataxia. He did not have any tonsillary tissue. The diagnosis of ataxia-telangiectasia was made and confirmed by demonstration of elevated levels of α -fetoprotein, low immunoglobulins, and increased radiation sensitivity of the chromosomes. The patient has had no infections since immunoglobulin replacement therapy was initiated. This patient could have been diagnosed early, probably before the hearing loss occurred, had the physicians who took care of him been aware of such condition.

Among PIDs, severe combined immunodeficiency (SCID) is unique in a sense that if unrecognized, mortality is almost 100% before the first birthday. SCID babies usually appear healthy at birth, and then start having infections in the first few months of life. These infections are not really mild or local infections. Rather, they are severe, chronic, and systemic infections leading to complications, failure to thrive, and even death. To achieve a survival rate as high as 94%, these infants must be diagnosed and treated before they develop infections.

Fig. 1 Ocular telangiectasia and granulomatous dermatitis on the arms of a boy with ataxia-telangiectasia who presented with recurrent respiratory tract infections



Recurrent Otitis Media and Primary Immunodeficiencies

Otitis media is one of the most common infections in the first years of life [1, 2]. It is also the most common reason for children to be seen by a pediatrician [3]. In the past decades, it has been noted that early-onset acute otitis media (AOM) and the prevalence of recurrent otitis media in preschool children in the United States have been increasing [4, 5]. This increase is thought to be associated with higher day care attendance and a higher prevalence of atopy. Recent reviews concluded that although the relationship between otitis media and atopy is not well-understood, patients with otitis media with effusion should be considered for allergy evaluation [6].

Recurrent otitis media is defined as three or more episodes of AOM in 6 months, or four episodes in 1 year with asymptomatic periods in between. A major factor that predisposes infants to otitis media is eustachian tube dysfunction that is more severe during upper respiratory tract infections. Children who attend day care may develop an average of 9 to 10 respiratory infections per year, more than 60% of which were complicated by AOM and/or otitis media with effusion [7, 8]. Impaired eustachian tube function can also be seen temporarily in other conditions such as gastroesophageal reflux and allergic rhinitis. Other risk factors for developing otitis media in infants include bottle propping, chronic sinusitis, ciliary dysfunction, cleft palate, other craniofacial abnormalities, chromosomal abnormalities, and primary or secondary immunodeficiencies. Interestingly, formula feeding, use of pacifier, and exposure to second-hand smoke have been inconsistently identified as risk factors [9•].

PIDs can contribute to development of recurrent otitis media. They present a heterogeneous group of more than 180 disorders [10••] and are associated with increased risk of frequent infections, autoimmune disorders, and malignancy. The frequency of PIDs is estimated at about 1 in 10,000 worldwide [11–13]. Most PIDs are monogenic. To date, mutations in more than 150 genes have been linked to different types of PIDs [14••]. Severity of symptoms and complications of PIDs vary significantly and range from minor, as in selective IgA deficiency, to life-threatening, as in SCIDs.

The classification of PIDs is based on the primarily affected component of the immune system (Table 1). Defects in adaptive immune system include antibody deficiency syndromes and combined immunodeficiencies (CIDs). Defects of the innate immune system comprise disorders of phagocytes, Toll-like receptor-mediated signaling defects, and complement deficiencies. Other PIDs include diseases of immune dysregulation, autoinflammatory conditions, and other well-defined immunodeficiency syndromes in which other clinical features are present in addition to immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, and ataxia-telangiectasia).

Increased susceptibility to infections is the common characteristic of all these classes of PIDs. However, depending on the nature of the underlying immune defect, the locations of the infections and types of pathogens vary. In predominantly antibody deficiencies, patients usually have infections with encapsulated bacteria, including *Streptococcus*, *Moraxella*, and *Haemophilus spp*, that typically involve the upper and lower respiratory tract (otitis, sinusitis, and pneumonia). Several studies showed that recurrent otitis and sinusitis occur in 70% to 98% of patients with primary antibody deficiency [15, 16]. Antibody deficiency starting before 1 year of age suggests transient hypogammaglobulinemia or the most common genetic form of antibody deficiency, X-linked agammaglobulinemia. The latter is caused by mutations in the *Btk* gene that lead to absence of B cells and antibody production. The symptoms appear between 4 and 8 months of age, as transplacentally acquired IgG begins to wane [17]. These patients usually have no lymphoid tissue; therefore, absence of tonsils and palpable lymph nodes in a boy with recurrent respiratory infections should raise suspicion of X-linked agammaglobulinemia.

Common variable immunodeficiency is the most common symptomatic PID. It is defined clinically by the presence of recurrent infections and low levels of IgG (at least 2 SD below the mean) and at least one other immunoglobulin isotype, as well as by a failure to mount specific antibody response to challenge with vaccination or natural infection [18]. Patients usually present in the second or third decades of life.

Among antibody deficiencies, selective IgA deficiency is the most common form of PID, with a frequency of 1 in

Table 1 Classification of primary immunodeficiencies

Primary immunodeficiency	Examples
Predominantly antibody deficiencies	Btk deficiency, CVID
Combined T- and B-cell immunodeficiencies	γ c deficiency, JAK3 deficiency, Omenn syndrome
Other well-defined immunodeficiency syndromes	WAS, AT, DiGeorge syndrome, hyper-IgE syndromes
Diseases of immune dysregulation	Chédiak-Higashi syndrome, perforin deficiency, XLPs
Congenital defects of phagocyte number, function, or both	Severe congenital neutropenia, X-linked and autosomal recessive CGDs
Defects in innate immunity	WHIM syndrome, herpes simplex encephalitis
Autoinflammatory disorders	FMF, TRAPS, NOMID
Complement deficiencies	C1–C9 deficiencies, MBP deficiency

AT ataxia-telangiectasia, *Btk* Bruton tyrosine kinase, *CGD* chronic granulomatous disease, *CVID* common variable immunodeficiency, *FMF* familial Mediterranean fever; γ c common γ chain, *JAK3* Janus kinase 3, *MBP* mannose-binding protein, *NOMID* neonatal-onset multisystem inflammatory disease, *TRAPS* tumor necrosis factor receptor–associated periodic syndrome, *WAS* Wiskott-Aldrich syndrome, *WHIM* warts, hypogammaglobulinemia infections, myelokathexis, *XLP* X-linked lymphoproliferative syndrome

(Data from Notarangelo et al. [10•].)

600 individuals. It is often found incidentally during screening of healthy blood donors [11] or for celiac disease (in which IgA deficiency is more prevalent). Although most patients are asymptomatic, selective IgA deficiency is also associated with a higher incidence of respiratory tract infections, including otitis media [19].

In children whose symptoms are suggestive of antibody deficiency but with normal immunoglobulin levels, specific antibody deficiency should be considered. Patients with specific antibody deficiency have normal levels of total immunoglobulins, but an inability to make antibodies against polysaccharide antigens is present. We can assess this by checking antibodies against polysaccharide vaccines (usually the 23-valent pneumococcal vaccine) 4 to 6 weeks after vaccination [20].

CIDs are associated with impaired development, function, or both of T and B lymphocytes. The deficient antibody production may result from intrinsic defects in B cells or may reflect T-cell deficiency. The presentation of symptoms depends on the severity of the defect. In SCID, the most severe form of CID, there is profound deficiency of peripheral T lymphocytes [21]. These patients present in the first few months of life with severe infections caused by opportunistic microorganisms as well as common viruses and bacteria. They may have otitis media, but because of the severity of the immunologic defect, these patients are more likely to develop fulminant systemic infections rather than local infections. Other PIDs associated with recurrent infections were previously discussed elsewhere [22•, 23•].

Because otitis media is so common in infants, how can we decide to further evaluate our patients for PIDs? First of all, in an otherwise healthy, normal-growing infant, more common causes, such as anatomic abnormalities, day care attendance, and allergies, should be sought. However, if the infant presents with certain associated findings summarized

in Table 2, then immunologic evaluation should be initiated immediately. These patients may also show some warning signs, including progression of the infections to mastoiditis, abscesses, sepsis, or meningitis, and persistence of the infections despite adequate treatment. In our clinic, patients who are referred for evaluation for recurrent otitis media undergo a detailed history and careful physical examination. Then we obtain complete blood count with differentials, quantitative IgG, IgM, IgA, and IgE, and specific antibody response to protein and polysaccharide antigens, as well as allergy skin testing. Of note, allergy skin testing will also help us detect endogenous antibody production and isotype switching. If the skin prick test is positive, then we can say that the patient's immune system is capable of isotype switching and producing specific antibodies [24].

Severe Combined Immunodeficiency

Among PIDs, SCID is the most serious and lethal form. The prevalence of SCID is estimated between 1 in 40,000 and 1 in 100,000 live births. These infants develop failure to thrive, chronic diarrhea, and infections in the first few months of life. Infections can occur with common pathogens, but most of the time, infants also suffer opportunistic infections such as candidal thrush or *Pneumocystis jiroveci* pneumonia. Graft-versus-host disease caused by maternal T-cell engraftment may occur in these patients and present with skin rash and organomegaly.

Mutations in at least 15 different genes have been linked to different forms of SCID [14•], and more novel genes and molecular mechanisms will be discovered. X-linked SCID, which is caused by defects in common γ chain, accounts for about 45% of all cases in the United States [25]. SCID is also caused by mutations in the genes that

Table 2 Associated findings, diagnostic tests, and treatment options in PID patients who present with recurrent otitis media

PID	Age at onset	Associated findings	Diagnostic tests	Treatment
Combined T- and B-cell immunodeficiencies	First 2–3 mo of life	FTT, opportunistic infections, chronic diarrhea, severe life-threatening infections, rash	CBC with differentials, immunoglobulins, lymphocyte subsets by flow cytometry, lymphocyte proliferation assay, genetic testing	Prophylactic antibiotics, antifungals, immunoglobulin replacement, HSCT, gene therapy
Predominantly antibody deficiencies	After 4–6 mo of age	Recurrent upper and lower airway infections, autoimmune diseases, allergy	Immunoglobulins, IgG subclasses, antibody response to antigens	Immunoglobulin replacement (IVIG or SCIG), prophylactic antibiotics
DiGeorge syndrome	Birth in severe cases	Cleft palate, congenital heart disease, hypocalcemia, upper and lower respiratory tract infections	CBC with differentials, immunoglobulins, serum calcium, cardiac echocardiogram, FISH	Prophylactic antibiotics, immunoglobulin replacement, thymus transplantation or HSCT in complete DiGeorge syndrome
Wiskott-Aldrich syndrome	First 4–6 mo of age	Petechia, bleeding, eczema, thrombocytopenia, small platelets	CBC with differentials, platelet volume, immunoglobulins, Wiskott-Aldrich syndrome protein analysis by flow cytometry, mutation analysis	Prophylactic antibiotics, immunoglobulin replacement, HSCT, gene therapy
Ataxia-telangiectasia	After 4–6 mo of age	Ataxia (patients can be diagnosed with cerebral palsy), recurrent pneumonia, aspirations, telangiectasia after 6 y of age	Serum α -fetoprotein level, immunoglobulins, CBC with differentials, radiation sensitivity assay, ataxia-telangiectasia gene mutation analysis	Prophylactic antibiotics, immunoglobulin replacement, physical therapy
Hyper-IgE syndrome	Usually during infancy	Rash, pneumonia, fractures, bone and teeth abnormalities, abscesses	CBC with differentials, serum IgE, <i>STAT3</i> and <i>DOCK8</i> mutation analysis	Prophylactic antibiotics
Congenital defects of phagocyte number, function, or both	Usually during infancy	Abscesses of skin, lymph nodes, liver, lung; delayed separation of umbilical cord; gingivitis; oral ulcers	CBC with differentials, DHR, flow cytometry for CD11abc, CD18	Antibiotics, HSCT in CGD, GCSF in neutropenia

CBC complete blood count, CGD chronic granulomatous disease, DHR dihydrodramine test, DOCK8 dedicator of cytokinesis 8, FISH fluorescence in situ hybridization, FTT failure to thrive, GCSF granulocyte cell-stimulating factor, HSCT hematopoietic stem cell transplantation, IVIG intravenous immunoglobulin, PID primary immunodeficiency, SCIG subcutaneous immunoglobulin, STAT3 signal transducer and activator of transcription 3

encode adenosine deaminase (*ADA*), Janus kinase 3 (*JAK3*) [26], interleukin-7 receptor α chain [27], recombina-se-activating genes 1 or 2 (*RAG1* or *RAG2*) [28], *CD45* [29], Artemis [30], ligase IV [31], DNA protein kinase catalytic subunit (*DNA-PKcs*), *CD3 δ* , *CD3 ϵ* , or *CD3 ζ* [32], all of which are inherited as autosomal recessive traits [33•]. T-lymphocyte development and function are severely compromised in all forms of SCID. Different combinations of T, B, and natural killer (NK) cell counts characterize different forms of SCID: TB^-NK^- , TB^+NK^- , TB^-NK^+ , and TB^+NK^+ . In addition, without normal T-helper (Th) lymphocytes (eg, Th1, Th2, regulatory T cells, Th17), B lymphocytes, macrophages, and residual T lymphocytes cannot function, even if they are normal in number [34, 35]. Regardless of the immunologic phenotype, SCID patients have similar clinical presentations, including early-onset respiratory tract infections, failure to thrive due to chronic diarrhea, and oral and genital *Candida* spp infections.

Regardless of the genetic defect, all patients share a common characteristic: low levels of absolute lymphocyte counts (ALCs) due to complete absence or extremely low levels of T cells, which normally constitute 70% of total circulating lymphocytes. These patients have severe defects in cellular and humoral immunity that result in increased susceptibility to severe and recurrent infections. Almost all patients could be diagnosed at birth if routine ALCs were checked and flow cytometry was performed when the ALC was below 2,500/ μL [36, 37].

SCID is considered as a pediatric emergency. Mortality is 100% in infancy without prompt immune reconstitution through hematopoietic stem cell transplantation, enzyme replacement, or gene therapy [38–41]. It has been well-known that the chances of successful treatment are highest in infants who have not yet experienced severe opportunistic infections [39]. A recent study demonstrated that SCID patients diagnosed at birth because of a positive family history have a significantly improved outcome compared with the first presenting family member (overall survival, 90% vs 40%) [42]. Another study showed that the survival rate was 94% in infants who received a bone marrow transplant in the first 3.5 months of life, whereas it was 70% for the infants who were transplanted after 3.5 months [43].

Unfortunately, physicians suspect SCID in their patients after the infants have already suffered recurrent and often serious infections. At that time, however, even though a correct treatment is initiated, permanent sequelae caused by the severe infections (eg, meningitis, encephalitis, and pneumonia) have already occurred. Furthermore, many infants die before the diagnosis of SCID is made. Recently, another concern has been raised about the risk of administration of live rotavirus vaccines to these infants [44, 45]. Diagnosing SCID early in life also improves long-term prognosis [43, 46].

A recent family survey–based evaluation identified a mean delay of 3.5 months from the onset of symptoms to diagnosis [47]. The delay in diagnosis can be explained by several factors: the infants usually appear healthy at birth, most patients have no family history of immunodeficiency, and the most common presenting symptoms—infections—are common problems in the general population. This survey also demonstrated that testing of infants at birth had a statistically significant positive impact on survival (85% of those tested at birth, compared with 58% of those not tested). Therefore, a population-based newborn screening (NBS) program could be the correct approach to diagnose and treat these infants early.

Newborn Screening for Severe Combined Immunodeficiency

NBS has been a standard component of care for many years. States that implement NBS will have to decide for which conditions they will screen. The disorder should be clinically and biochemically well-defined; there must be a reliable means to confirm the diagnosis after a positive NBS; the condition should be associated with known significant morbidity and mortality; and, finally, it is most important that effective treatment that improves the outcome be available. SCID is important to consider for inclusion on the list of conditions in the NBS for the following reasons: 1) most newborns with SCID appear healthy at birth, 2) untreated patients die within the first year of life, 3) the condition can be cured if recognized early, 4) markers of SCID can be detected in the newborn dried blood spot, and 5) a simple confirmatory test using flow cytometry to evaluate lymphocyte subsets is available [48].

Because all SCID patients have low numbers of T cells, they are all lymphopenic, even at birth. Therefore, recognition of low ALC results in early diagnosis [49]. Development of an NBS test to detect low numbers of T cells would be the most practical approach. In 2005, Dr. Jennifer Puck developed a screening method for SCID based on measurement of T-cell receptor excision circles (TRECs) by polymerase chain reaction, using DNA extracted from newborn dried blood spots [48]. TRECs are byproducts of V(D)J recombination generated during normal T-cell maturation and consist of circular signal joints. They are exported to the periphery by newly generated T lymphocytes that leave the thymus. Therefore, the levels of TRECs in T cells are particularly high in healthy newborns. Conversely, they are undetectable or present in very low numbers in newborns with SCID. Discovery of this screening method has been a major step in recognizing these infants at birth. In 2008, Wisconsin

became the first state to screen all newborns for SCID using Dr. Puck's method [50]. By December 2008, 71,000 infants were screened by the TREC assay in the state of Wisconsin. Seventeen infants had at least 1 abnormal TREC assay (TREC values $<25/\mu\text{L}$). A total of eight infants were confirmed to have T-cell lymphopenia by flow cytometry. The causes of the T-cell lymphopenia were DiGeorge syndrome ($n=2$), idiopathic T-cell lymphopenia ($n=2$), extravascular extravasation of lymphocytes ($n=3$), and a *Rac2* mutation ($n=1$). The infant with the *Rac2* mutation underwent successful cord blood transplantation [50].

Currently, Wisconsin, Massachusetts, California, New York, Louisiana, and Puerto Rico provide for universal SCID screening. The commonwealth of Massachusetts embarked on a pilot program universally offering NBS for SCID in 2009 [51]. In 2010, the first case of SCID was reported after screening 100,597 infants in Massachusetts [52]. The patient was found to have Janus kinase 3 deficiency. The infant was immediately isolated to reduce the risk of opportunistic infections. In this report, 78 (0.08%) other infants had the NBS test result come back as suggestive of SCID. Based on the lymphocyte phenotyping by flow cytometry in these screen-positive children, only 29 (0.03%) infants required a clinical evaluation, among whom the patient with SCID was identified. The low rate of false-positive results supports the favorable cost/benefit ratio of this screening protocol. On May 21, 2010, the secretary of Health and Human Services announced the addition of SCID to the core NBS panel of 29 genetic disorders.

Recently, three siblings with autosomal recessive hyper-IgE syndrome caused by dedicator of cytokinesis 8 (*DOCK8*) mutation were found to have an undetectable or reduced number of TRECs. This report suggests that autosomal recessive hyper-IgE syndrome may be detected by TREC NBS, and this diagnosis should be considered in the evaluation of newborns with abnormal TRECs who do not have typical SCID [53].

Another method, tandem mass spectrometry, has been instituted for diagnosis of adenosine deaminase deficiency, one of the most frequently occurring forms of SCID, at a negligible cost. A pilot population-based NBS for adenosine deaminase-SCID has started in Tuscany, Italy. Initial results revealed that adenosine deaminase deficiency seems to be more common than previously thought [54].

Conclusions

PIDs are considered to be one of the causes of recurrent otitis media in children. Individual PIDs may be rare, but as a group, PIDs are common. Among these, SCID is considered as a pediatric emergency, as these infants die

within the first year of life unless immune reconstitution is established early. Morbidity, delayed diagnosis, increased medical costs, and death were potentially avoidable outcomes with the institution of a universal NBS test. Until NBS test becomes widely available, pediatricians can use absolute lymphocyte counts to screen their patients for SCID. During the newborn period, any ALC less than $2,500/\mu\text{L}$ should be evaluated for SCID by first repeating the test and then by performing flow cytometry to check T-cell counts. If neonatal screening becomes available to every neonate, then definitive treatment can be initiated immediately, which would result in up to 94% survival [43]. In addition, NBS would reveal other conditions associated with T-cell deficiency and the true incidence of SCID [50, 53, 54].

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