Pediatr Pol 2026; 101 (1): 8-16
DOI: https://doi.org/10.5114/polp.2026.159958
Submitted: 21.06.2025, Accepted: 05.10.2025, Published: 09.03.2026

PEDIATRIA Polska
PISMO POLSKIEGO TOWARZYSTWA PEDIATRYCZNEGO
Polish Journal of PAEDIATRICS
OFFICIAL JOURNAL OF POLISH SOCIETY OF PAEDIATRICS

ORIGINAL PAPER

What the pediatrician should know about different types of severe combined immunodeficiency: a single-center experience

Nel Dąbrowska-Leonik[1], Barbara Piątosa[2], Nadezda Bohynikova[1], Renata Grzywa-Czuba[3], Beata Wolska-Kuśnierz[1], Katarzyna Bernat-Sitarz[1], Małgorzata Skomska-Pawliszak[1], Ewa Anna Bernatowska[1], Małgorzata Pac[1]

[1]Department of Immunology, The Children's Memorial Health Institute, Warsaw, Poland
[2]Histocompatibility Laboratory, The Children's Memorial Health Institute, Warsaw, Poland
[3]Department of Clinical Microbiology and Immunology, The Children's Memorial Health Institute, Warsaw, Poland

ABSTRACT

Introduction: Severe combined immunodeficiency (SCID) is the most serious inborn error of immunity, lethal if untreated. There are three SCID subtypes: typical (TS), atypical (AS) and Omenn syndrome (OS). The goal of this study is to characterize clinical and immunogenetic aspects of patients with different aforementioned types of SCID diagnosed in a single center and an attempt to select factors improving diagnosis in the areas without newborn screening.

Material and methods: This is a retrospective evaluation of the clinical course and hematological, biochemical, immunological and genetic tests leading to SCID diagnosis in 42 children.

Results: Median age of diagnosis was 4.4 months, higher for AS (8 months, $p < 0.05$). Median diagnostic delay (DD) was 2.5 months (4.7 months in AS children). Suspicion of the disease was raised by pediatricians (in 44.4% of all children), hematologists (19.4% of all children, 26.3% of AS children, with DD of 20 months), or dermatologists. The first symptoms were infections (64%), rash (22.2%), chronic diarrhea (5.6%), anemia (5.6%) and lymphopenia (2.8%). At the time of diagnosis, 79.5% of patients presented with lymphopenia. The median of recent thymic emigrants was 0.2%, 2.1%, 0.3% in TS, AS and OS, respectively. The most frequent pathogenic variants were found in the following genes: IL2RG (23.8%), RAG1/2 (16.6%), JAK3 (14.3%), ADA (11.9%) and IL7RA (4.8%). The overall survival rate was 69% in all children.

Conclusions: The diagnosis of SCID was established significantly later in the case of AS than TS and OS. The type of first symptoms does not differ between particular types of SCID. Lymphopenia is the most common symptom and the most often underestimated laboratory sign of SCID.

KEY WORDS:

specialist, Omenn syndrome, lymphopenia, immunoglobulin M, atypical SCID.

INTRODUCTION

Severe combined immunodeficiency (SCID) is the most profound inborn error of immunity affecting cellular and humoral immunity. If left untreated, the disease leads to death in the first years of life, mainly due to infections, including opportunistic ones. Affected infants appear healthy at birth however usually develop life-threatening bacterial, viral, fungal or opportunistic infections, persistent diarrhea and failure to thrive within the first weeks

ADDRESS FOR CORRESPONDENCE:

Nel Dąbrowska-Leonik, MD, Department of Immunology, The Children's Memorial Health Institute, Warsaw, Poland, e-mail: n.dabrowska-leonik@ipczd.pl

and months of life. The clinical manifestations of SCID include recurrent upper and lower respiratory tract infections caused by common pathogens with an atypical course and complications such as:

- chronic rhinitis,
- recurrent, chronic lower respiratory tract infections, e.g. caused by adenoviruses or parainfluenza viruses,
- urinary tract,
- diarrhea.

The most dangerous are infections caused by opportunistic pathogens (i.e. *Pneumocystis jiroveci*, cytomegalovirus – CMV, or fungi):

- recurrent thrush,
- symptomatic CMV infection with lung, liver, central nervous system involvement,
- aspergillosis with systemic or organ involvement (lung, liver, spleen, central nervous system, bones).

Routine immunization with live attenuated vaccines such as BCG (*Bacillus Calmette-Guérin*) vaccine or rotavirus are the cause of local or disseminated infection.

Following all infections infant's physical development is inhibited.

The next red flags are signs including non-infectious presentation (skin rashes, lymphadenopathy, hepatomegaly, splenomegaly) and abnormalities in diagnostic tests (i.e. lymphopenia, but also lymphocytosis, eosinophilia, elevated IgE, thymus absence and/or skeletal abnormalities) and also a family history of infants' or young children's deaths or immunodeficiencies. Depending on the clinical symptoms and laboratory test results, there are three SCID subtypes: typical, atypical (leaky) and Omenn syndrome (OS) as shown below in diagnostic criteria [1]. Early diagnosis, before the onset of severe infections and organ damage, is possible in children with a positive family history or through newborn screening (NBS) and is crucial for overall survival [2]. The awareness of SCID and early recognition of the first symptoms are extremely important in the case diagnosis without access to NBS or positive family history. The aim of this study is to characterize patients diagnosed with different types of SCID according to clinical and immunogenetic phenotypes in a single center and to select the factors that could help improve SCID diagnosis in the areas without NBS.

MATERIAL AND METHODS

PATIENTS

This study included 42 Caucasian children (16 girls and 26 boys), aged 6 days to 48 months, diagnosed with SCID in the Department of Immunology, Children's Memorial Health Institute, Poland, between 2010 and 2023. The clinical course as well as hematological, biochemical, immunological and genetic tests leading to SCID diagnosis were evaluated retrospectively. None of the patients received NBS for SCID, however 6 had a positive family history.

QUANTITATIVE AND FUNCTIONAL ASSESSMENT OF CELLULAR AND HUMORAL IMMUNITY

Lymphocyte subsets

Analysis of lymphocyte subsets was performed using commercially available BD Multitest six color cocktails of antibodies and Trucount tubes (Becton Dickinson, cat. No. 644611). The assessed lymphocyte subset panel included T-cells (CD3+/CD45+), cytotoxic T-cells (CD3+CD8+/CD45+), helper T-cells (CD3+CD4+/CD45+), NK-cells (CD16+CD56+CD3–/CD45+), and B-cells (CD19+/CD45+). Their distribution and absolute cell counts were determined using the lyse-no-wash approach. The staining procedure was performed according to the manufacturer's instructions. Identification of lymphocyte subsets was performed according to standard procedures. The absolute number of individual subsets was calculated based on the proportion of the respective cell subpopulation and absolute lymphocyte count. Results have been compared to normal age-related reference ranges. Recent thymic emigrants (RTE) – CD31+CD45RA+/CD3+CD4+, within T-helper cell population were analyzed separately, and results compared to local reference ranges [3].

Lymphocyte transformation test

Peripheral blood mononuclear cells were cultured in Roswell Park Memorial Institute 1640 medium supplemented with 10% heat inactivated fetal bovine serum, in 3 replicates: without mitogen (control), with phytohemagglutinin (PHA), and with anti-CD3 monoclonal antibody, to evaluate different mechanisms of T-cell stimulation [4]. Incorporation of 3H-thymidine into proliferating lymphocytes was used to measure the lymphoproliferative response to tested stimulants [5]. Mean counts per minute (cpm) and standard deviation were calculated for 3 replicates for cultures with or without the tested stimulants. The stimulation index (SI) measuring the response of the tested cells in relation to unstimulated controls was counted to normalize the intra- and inter-individual variations in the background of the cell proliferation. The obtained results have been compared to normal values PHA (≥ 16000 cpm, SI: ≥ 65) and anti-CD3 (≥ 15000 cpm, SI: ≥ 60).

Immunoglobulin class G (IgG) and M (IgM) were determined by nephelometry on automated BN ProSpec and Atellica® NEPH 630 Siemens Healthineers (since 2019) using high specificity monoclonal antibodies, and results were compared to local reference ranges [6].

MOLECULAR DIAGNOSTICS

The molecular diagnostics included whole gene direct Sanger sequencing or next-generation sequencing (NGS) for the primary immunodeficiency gene panel with confirmatory Sanger sequencing in the targeted region,

performed in different genetic laboratories (Department of Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; Department of Medical Genetics, Medical University of Warsaw; MedGen Medical Centre, Warsaw, Poland).

DIAGNOSTIC CRITERIA

The Primary Immune Deficiency Treatment Consortium criteria were used to make the diagnosis of SCID: typical SCID (TS), leaky/atypical SCID (AS) and OS [1], as follows:

1. Typical SCID:

- absence or a very low number of T-cells (< 0.05 × 10^9/l) and pathogenic gene variant or no alternate explanation for low T-cell count and < 20% of CD4+ T-cells have naïve cell surface markers (or undetectable/low T-cell receptor excision circles – TRECs),
- or the presence of T-cells of maternal origin (transplacentally acquired maternal engraftment – TME).

2. Leaky/atypical SCID:

- two or more of: reduced number of CD3+ T-cells (0.05–1.0 × 10^9/l for children < 2 years of age, < 0.8 × 10^9/l if aged 2–4 years, < 0.6 × 10^9/l any age); oligoclonal T-cells; < 20% of CD4+ cells are naïve (or abnormal TRECs),
- pathogenic gene variant or reduced proliferation (response to PHA, anti-CD3, or anti-CD3/CD28 < 50% lower limit of the reference range),
- and does not have: other SCID subtype, combined immunodeficiency with known genotype, thymic disorder, other disorder with low T-cell numbers.

3. Omenn syndrome:

- generalized skin rash plus absence of TME,
- pathogenic gene variant, however we also included 3 patients without pathogenic variants due to limited access to genetic diagnostics,
- > 80% of CD4+ T-cells have CD45RO+ memory phenotype,
- two or more of: eosinophilia (> 0.8 × 10^9/l), elevated IgE, abnormal TRECs, lymphadenopathy, hepatomegaly and/or splenomegaly, oligoclonal T-cells.

The exclusion criteria were congenital athymia, as well as combined immunodeficiencies with known genotype, and other disorders with low T-cell counts [1, 7].

STATISTICAL ANALYSIS

Statistical analysis was carried out using the TIBCO Statistica version 13.3 software (TIBCO Software Inc., Santa Clara, CA, USA). The data distribution was not normal which was confirmed with the Shapiro-Wilk normality test. The data comparison between the three groups was carried out using the Chi^2 Pearson test for nominal data and the Kruskal-Wallis test for ordinal and quantitative variables. Statistically significant results were estimated at $p < 0.05$.

RESULTS

Between 2010 and 2023, SCID was diagnosed in 42 children (16 females and 26 males), including: 17 TS, 19 AS, and 6 OS. In 36 children, diagnosis was made after the onset of symptoms at a median age of 6 months, ranging 2–48 months. The median age of first symptoms was 2 months. Six children had a positive family history and were diagnosed mostly in the first 2 weeks of life, before the onset of symptoms. Typical SCID was diagnosed in 17 children: in 5 with a positive family history and in another 12 after the onset of symptoms. Atypical SCID and OS were diagnosed in 19 and 6 children, respectively. In children with AS, the first symptoms appeared later, at a median age of 4.9 months and were diagnosed significantly later, at a median age of 8 months. Median diagnostic delay (DD) was 2.5 months: 2.4 months in TS, 1.7 month in OS and 4.7 months in children with AS (Table 1). Children were referred for further diagnostics mainly by pediatricians (44%). Hematologists suspected SCID in approximately 20% of all patients, and in more than 25% of children with AS. About 60% of patients with OS were referred by dermatologists (Table 2). The diagnostic delay varied depending on the referring specialist and was longer for patients referred by hematologists: median 20 months (Table 3).

The first manifestations were infections (64% of children with symptomatic SCID and 83% of children with symptomatic TS), rash (22.2% of all symptomatic children and 80% of children with OS), chronic diarrhea (5.6%), anemia (5.6%) and lymphopenia (2.8%); no statistically significant differences between SCID subtypes were found (Table 2).

INFECTIONS

The most commonly reported complication was local or disseminated BCG infection following the mandatory vaccination within the first 48 hours of life. Over 50% of vaccinated patients (18 out of 32) experienced BCG-related complications, including 5 (16%) who developed disseminated BCG infection. Children required anti-tuberculosis treatment in accordance with Polish and European guidelines [8, 9]. This infection occurred more often in TS than in AS and OS: 83%, 44% and 25%, respectively (Table 2).

Other bacterial and fungal infections, including opportunistic ones, were less common (Table 2). Gastrointestinal infections occurred sporadically and were not included in the analysis.

NON-INFECTIOUS SYMPTOMS

Skin rash remained the first and main symptom in 8 patients. Exfoliative erythroderma with eosinophilia was the first manifestation in 4 infants, and 3 of them,

TABLE 1. Demographic features and laboratory results in typical severe combined immunodeficiency (12 symptomatic and 5 with a positive family history), atypical severe combined immunodeficiency and Omenn syndrome (1 with a positive family history)

Parameters	SCID, median (quartiles: Q1; Q3)	TS, median (quartiles: Q1; Q3)	AS, median (quartiles: Q1; Q3)	OS, median (quartiles: Q1; Q3)	*p*-value
Age of first symptoms (months)	2.0 (0.93; 6)	2.0 (1.2; 4.7)	4.9 (1.7; 8)	0.9 (0.3; 1)	0.0181
Age of diagnosis (months)	4.4 (2.5; 8.8)	3.0 (0.5; 7.5)	8 (4; 20.2)	2.3 (1.8; 2.8)	0.0011
Diagnostic delay (months)	2.5 (1.2; 7.1)	2.4 (1.3; 3.4)	4.7 (1.1; 19)	1.7 (1.6; 1.8)	0.2798
IgM [g/l]	0.23 (0.09; 0.74)	0.19 (0.07; 0.26)	0.61 (0.22; 1.85)	0.14 (0.05; 0.51)	0.0160
PHA [SI]	3.3 (1.1; 11.1)	1 (1; 1.7)	11.1 (5.6; 20.7)	8.8 (5; 12.5)	0.0001
Anti-CD3 [SI]	6.9 (1.3; 16.1)	1.1 (1; 1.4)	15.3 (9.3; 37.5)	11.05 (4.95; 15.2)	0.0005
RTE (%)	0.95 (0.2; 3.5)	0.2 (0; 1.3)	2.1 (0.6; 5.9)	0.3 (0.1; 0.5)	0.1387

AS – atypical severe combined immunodeficiency, IgM – immunoglobulin class M, OS – Omenn syndrome, RTE – recent thymic emigrants, PHA – phytohemagglutinin, SCID – severe combined immunodeficiency, SI – stimulation index (references values of SI for PHA were ≥ 65 and for anti-CD3 ≥ 60), TS – typical severe combined immunodeficiency

ultimately diagnosed with Omenn syndrome, were referred by the dermatologist quite quickly – median DD of 1 month. The other 5 children with skin rash were diagnosed after the onset of infection, although 4 of them (80%) had lymphopenia in an earlier assessment.

Severe anemia, mostly autoimmune hemolytic anemia (AIHA), was the reason for the hematological evaluation and treatment in 7 patients. All of them also presented with lymphopenia, but it was the reason for further immunological assessment only in 2 of them (age of diagnosis – AD, 2–5 months; DD 1–2 months). The other 5 children were diagnosed with AS later, when severe infections appeared: recurrent pneumonia in 4 children, and toxoplasmic retinitis leading to loss of vision in 1 patient (AD 3–48 months; DD 2–42 months). Among them, 4 children had a high IgM level (ranging 1.85–6.83 g/l). In 3 of them, genetic diagnostics showed the same homozygous variant in the *RAG1* gene (c.256_257delAA), known as the Vistula watershed variant [10].

Isolated lymphopenia led to the suspicion of SCID only in 1 patient, meanwhile at the time of SCID diagnosis, 80% of patients presented with lymphopenia in the blood count, which was significantly more profound in children with TS and AS than with OS (Table 2). Neutropenia and eosinophilia were less common, occurring in 36% and 31% of children, respectively.

IMMUNOLOGICAL AND IMMUNOGENETIC ASSESSMENT

The diagnosis of TS was made in 17 children according to the Primary Immune Deficiency Treatment Consortium [1], based on a T-cell count below 50 cells/ml and the exclusion of other causes of severe T-lymphopenia. Recent thymic emigrants were measured only in 3 patients due to a very low T-cell count (Table 1).

Atypical SCID was diagnosed in 19 patients, with the count of T-lymphocytes below 1000 cells/ml in 18 of them, RTE < 20% in 13/15 patients (median 2.1%), reduced lymphoproliferation in response to PHA < 50% of the lower limit of normal in 12/13 patients (median 11.1 SI, normal value > 65 SI) and reduced proliferation in response to anti-CD3 < 50% of the lower limit of normal in 10/13 children (median 15.3 SI, normal value > 60 SI) (Table 1).

Omenn syndrome was diagnosed in 6 children with generalized rash and the count of T-lymphocytes in the range of 106–80.943 cells/ml. Recent thymic emigrants were determined in 5 patients, all of them having values below 5%. Median lymphoproliferative response to PHA measured as SI was 8.8, and to anti-CD3 – 11.05 (reference values: 65 and 60, respectively). All 6 children with OS had eosinophilia, 4 out of 5 with elevated IgE levels. Three patients without a genetic diagnosis were included in this group due to limited genetic diagnostic possibilities.

Both IgG and IgM levels were below age reference values in 17.1% of patients, more often in TS – 23.5%, than in AS or OS – 11.1% and 16.7%, respectively. The IgM alone was below normal only in 45% of children, normal in 32.5% and elevated in 22.5%. High IgM was more frequently observed in children with AS (38.9%) than in typical forms (6.3%) or OS (16.7%), but no significant differences were found (Table 2).

Genetic diagnosis was available in 31 patients and revealed the most common pathogenic variants in the following genes: *IL2RG* (10 patients), *RAG1/2* (7 patients in total), *JAK3* (6 patients) and *ADA* (5 patients) (Table 2).

Thirteen out of 42 analyzed patients passed away until the end of 2024. Deaths occurred in one third of symptomatic patients and in 17% of patients with a positive family history. Four children succumbed before hematopoietic stem cells transplantation (HSCT) as a result of severe and overwhelming infections, and 9 died after HSCT: 5 of them due to infections and 4 due to non-infectious complications.

TABLE 2. Demographic features and laboratory results in typical severe combined immunodeficiency (12 symptomatic and 5 with a positive family history), atypical severe combined immunodeficiency and Omenn syndrome (1 with a positive history)

Parameters	SCID	TS	AS	OS	*p*-value (Pearson's χ^2 test)
Gender, *n*/*N* (%)					
Female	16/42 (38.1)	5 (29.4)	7 (36.8)	4 (66.7)	0.2681
Male	26/42 (61.9)	12 (70.6)	12 (63.2)	2 (33.3)	
Referring physician, *n*/*N* (%)					
Pediatrician	16/36 (44.4)	9/12 (75)	6/19 (31.6)	1/5 (20)	0.0126
Hematologist	7/36 (19.4)	1/12 (8.3)	5/19 (26.3)	1/5 (20)	
Dermatologist	3/36 (8.3)	0/12 (0)	0/19 (0)	3/5 (60)	
Anesthesiologist	4/36 (11.1)	1/12 (8.3)	3/19 (15.8)	0/5 (0)	
Infectious disease specialist	1/36 (2.8)	1/12 (8.3)	0/19 (0)	0/5 (0)	
Nephrologist	1/36 (2.8)	0/12 (0)	1/19 (5.3)	0/5 (0)	
Gastroenterologist	2/36 (5.6)	0/12 (0)	2/19 (10.5)	0/5 (0)	
Pulmonologist	1/36 (2.8)	0/12 (0)	1/19 (5.3)	0/5 (0)	
Cardiologist	1/36 (2.8)	0/12 (0)	1/19 (5.3)	0/5 (0)	
First symptoms, *n*/*N* (%)					
Pneumonia	11/36 (30.6)	4/12 (33.3)	7/19 (36.8)	0/5 (0)	0.1908
Aphthous stomatitis	2/36 (5.6)	2/12 (16.7)	0/19 (0)	0/5 (0)	
Encephalitis	2/36 (5.6)	1/12 (8.3)	1/19 (5.3)	0/5 (0)	
Recurrent respiratory tract infections	6/36 (16.7)	2/12 (16.7)	4/19 (21)	0/5 (0)	
BCGitis	1/36 (2.8)	1/12 (8.3)	0/19 (0)	0/5 (0)	
Chronic diarrhea	2/36 (5.6)	1/12 (8.3)	1/19 (5.3)	0/5 (0)	
Sepsis	1/36 (2.8)	0/12 (0)	1/19 (5.3)	0/5 (0)	
Skin rash	8/36 (22.2)	1/12 (8.3)	3/19 (15.8)	4/5 (80)	
Anemia	2/36 (5.6)	0/12 (0)	1/19 (5.3)	1/5 (20)	
Lymphopenia	1/36 (2.8)	0/12 (0)	1/19 (5.3)	0/5 (0)	
Infections, *n*/*N* (%)					
CMV	6/40 (15)	2/17 (11.8)	3/17 (17.6)	1/6 (16.7)	0.8842
BCG	18/32 (56.3)	10/12 (83.3)	7/16 (43.8)	1/4 (25)	0.1408
PJP	7/41 (17.1)	3/17 (17.6)	3/18 (16.7)	1/6 (16.7)	0.9966
Fungal etiology	13/34 (38.2)	8/13 (61.5)	5/15 (33.3)	0/5 (0)	0.0325
Bacterial etiology	20/39 (51.3)	5/17 (29.4)	10/16 (62.5)	5/6 (83.3)	0.0382
Lymphopenia, *n*/*N* (%)	31/39 (79.5)	15/17 (88.2)	14/16 (87.5)	2/6 (33.3)	0.0097
Neutropenia, *n*/*N* (%)	14/39 (35.9)	6/17 (35.3)	7/16 (43.8)	1/6 (16.7)	0.4977
Eosinophilia, *n*/*N* (%)	12/39 (30.8)	1/17 (5.9)	5/16 (31.3)	6/6 (100)	0.0001
IgM, *n*/*N* (%)					
Low	18/40 (45)	9/16 (56.3)	5/18 (27.8)	4/6 (66.7)	0.1375
Normal	13/40 (32.5)	6/16 (37.5)	6/18 (33.3)	1/6 (16.7)	
High	9/40 (22.5)	1/16 (6.3)	7/18 (38.9)	1/6 (16.7)	
IgG, *n*/*N* (%)					
Low	17/41 (41.5)	8/17 (47.1)	7/18 (38.9)	2/6 (33.3)	0.9697
Normal	19/41 (46.3)	7/17 (41.2)	9/18 (50)	3/6 (50)	
High	5/41 (12.2)	2/17 (11.8)	2/18 (11.1)	1/6 (16.7)	
Low IgG + IgM	7/41 (17.1)	4/17 (23.5)	2/18 (11.1)	1/6 (16.7)	0.6209

TABLE 2. Cont.

Parameters	SCID	TS	AS	OS	*p*-value (Pearson's χ^2 test)
Genetic defect, *n/N* (%)					
IL2RG	10/42 (23.8)	7/17 (41.2)	3/19 (15.8)	0/6 (0)	0.0695
JAK3	6/42 (14.3)	3/17 (17.6)	2/19 (10.5)	1/6 (16.7)	
ADA	5/42 (11.9)	2/17 (11.8)	3/19 (15.8)	0/6 (0)	
RAG1	3/42 (7.1)	0/17 (0)	3/19 (15.8)	0/6 (0)	
RAG2	4/42 (9.5)	0/17 (0)	3/19 (15.8)	1/6 (16.7)	
IL7RA	2/42 (4.8)	2/17 (11.8)	0/19 (0)	0/6 (0)	
Lig1	1/42 (2.4)	0/17 (0)	0/19 (0)	1/6 (16.7)	
Lack	11/42 (26.2)	3/17 (17.6)	5/19 (26.3)	3/6 (50)	

AS – atypical severe combined immunodeficiency, ADA – adenosine deaminase, BCG – Bacillus Calmette-Guerin, CMV – cytomegalovirus, IgG – immunoglobulin class G, IgM – immunoglobulin class M, IL2RG – interleukin 2 receptor subunit γ, IL7RA – interleukin-7 receptor α chain, JAK3 – Janus Kinase 3, OS – Omenn syndrome, PJP – pneumocystis jiroveci pneumonia, RAG1 – recombination-activating gene 1, RAG2 – recombination-activating gene 2, SCID – severe combined immunodeficiency, TS – typical severe combined immunodeficiency

TABLE 3. Severe combined immunodeficiency suspicion by specialist

Referring physician suspecting SCID diagnosis	Number of patients, *n* (%)	Age of diagnosis in months median (range)	Diagnosis delay in months median (range)	Number of patients TS/AS/OS
Pediatrician	16 (44)	5 (2–37)	2 (0–19)	9/7/1
Hematologist	7 (19)	21 (2–48)	20 (1–42)	1/5/1
Dermatologist	3 (8)	3 (2–3)	1 (1–2)	0/0/3
Gastroenterologist	2 (6)	16 (14–19)	9 (6–13)	0/2/0
Anesthesiologist/neonatologist	4 (11)	7 (4–9)	1 (0–1)	0/4/0
Cardiologist	1 (3)	4	1	0/1/0
Infectiologist	1 (3)	8	1	1/0/0
Pulmonologist	1 (3)	8	7	0/1/0
Nephrologist	1 (3)	15	13	0/1/0
All	36 (100)	6 (2–48)	2 (0–42)	12/19/5

AS – atypical severe combined immunodeficiency, OS – Omenn syndrome, SCID – severe combined immunodeficiency, TS – typical severe combined immunodeficiency

DISCUSSION

Severe combined immunodeficiency should be diagnosed as early as possible, as there is a greater chance of more effective treatment before severe infection and/or irreversible organ damage occur [2]. Patients with a family history of SCID are more likely to be diagnosed early. In our group, the survival rate of such infants was 83%, while the survival rate of the symptomatic patients was only 67%. We have observed progress in diagnostics for the last 3 decades. Comparing an earlier report (1993–2006) by Wolska-Kuśnierz [11] and our results, it is clear that in the later period both more patients (42 vs. 23) and at a younger age were diagnosed. The median age of SCID diagnosis decreased by 7–4.4 months, while the median DD was shortened by 5–2.5 months. It is worth emphasizing that the availability of immunological tests, including flow cytometry as well as genetic methods, has improved. In the earlier period, diagnosis was performed exclusively using the Sanger method and genetic confirmation was obtained only in 57% of patients (5 *IL2RG*, 3 *RAG1*, 3 *RAG2*, 1 *IL7RA*, and 1 *NHEJ1*). Currently, thanks to NGS, 74% of patients have genetic confirmation. However, there are still some goals to be achieved in terms of SCID diagnosis improvement.

It is known that early diagnosis is achievable with NBS for SCID. In Poland, there is no NBS program for SCID at the moment [12]. In a pilot Polish-German cross-border NBS study, among Polish infants, no cases of SCID were found, however 1 child with combined immunodeficiency and 1 with agammaglobulinemia were detected [13]. T-cell receptor excision circles-based screening for all newborns resulted in increased detection of infants with SCID and severe T-lymphocytopenia in many European countries [12]. In countries with no NBS program, SCID can be suspected either after the onset of symptoms or following a family history, which is extremely important in SCID patients [14]. That is why educating pediatricians and other specialists

about the first signs of SCID and positive family history is an important element of early diagnosis.

Severe combined immunodeficiency most frequently was suspected by pediatricians (up to 75% in the typical form), hematologists (over 25% in the atypical form) and dermatologists (60% of patients with Omenn syndrome). The diagnostic delay was shorter among patients referred by dermatologists, and concerned only a limited number of OS. It can be explained by a very severe clinical course including skin lesions not responding to treatment. The longer delay in diagnosis among patients referred by hematologists may result from a milder course (in most children with the atypical form) and presence of other causes of lymphopenia such as adverse drug reactions. There are no literature data on DD in SCID depending on the referring specialist. It is worth noting that currently the suspicion of the disease is established on the basis of NBS in many countries [12, 15].

In our cohort, recurrent, chronic or atypical infections were the first symptoms in 69% of all the children. The most common infection in this group of patients was BCG infection with a usually mild clinical course. This complication occurred significantly more often in children with TS than in those with AS and OS. The absolute counts of NK-cells did not influence the frequency of the local BCG reaction, but they seemed to play a role in protecting SCID patients against disseminated BCG complications, as reported previously by Bernatowska *et al*. [16] in another SCID group in Poland.

Retrospective analysis showed that 80% of all our SCID patients had pre-existing lymphopenia detected in blood count, but lymphopenia was the reason for SCID suspicion in only one patient. Lymphopenia is an important symptom of SCID and should not be underestimated if detected in an infant, even one who appears healthy. Flow cytometry analysis makes it possible to detect SCID before life-threatening symptoms and organ complications appear. Turkish neonatologists point out the need for diagnosis of SCID in newborns with lymphopenia, defined as a lymphocyte count below 3,000 cells/ml in a prospective study of 2,000 newborns [17]. The diagnosis of SCID should be considered in all infants with lymphopenia, particularly in the absence of a NBS program. It is extremely important when accompanied by the hypoplasia/absence of the thymus or bone dysplasia on chest X-ray. However, the absence of lymphopenia and normal immunoglobulin levels do not rule out the diagnosis of SCID. For example, children with *IL2RG* SCID might have normal lymphocyte counts in peripheral blood, but only B-lymphocytes are detected by flow cytometry, as was the case with one of our patients. Another explanation for lymphocytosis is transplacental maternal engraftment or oligoclonal lymphoproliferation in OS.

Immunoglobulin measurement rarely helps with the diagnosis of SCID. The immunoglobulin class G concentration might be within the reference values in the first months of age, because of its maternal origin. In our group, low IgG levels were detected only in 41.5%. Since low IgA can be found in healthy infants and young children up to 4 years of age, they are of limited diagnostic value. As already presented in the results, high IgM levels were observed in some symptomatic patients with no significant differences between all subtypes of SCID.

Both elevated IgM and IgG have been found in patients with *RAG* deficiency, autoimmunity and hyperinflammation in AS, OS and combined immunodeficiency. In *RAG*-deficient patients, impaired V(D)J recombination process leads to skewed repertoire of T- and B-cell receptors [18]. Additionally, the checkpoint in both T- and B-cell peripheral and central tolerance is broken and allows for the survival of cells with self-reactive specificity [19, 20]. High IgM levels were also reported by other authors. In a SCID group from India 19% had higher IgM levels [21].

The frequency of SCID genes varies in different populations. Pathogenic variants in the *IL2RG* gene are most common in our group of children (24%), as well as in the US population – 30%, German and Dutch population – 20% each [1, 22, 23], and dominant in the Chinese and Southeast Asian population [24, 25] – 53–73% of defects genetically confirmed. In the populations of Oman, Iran and Turkey, mutations in the *IL2RG* gene constitute less than 10% of identified SCID genes, while the most common genotype is *RAG1/2*, probably due to the higher incidence of consanguineous parents [26–28]. *RAG1/2* genes are also the most common causes of SCID in India, Italy, Serbia, and Montenegro [16, 29, 30].

CONCLUSIONS

In the study group, SCID diagnosis was established significantly later in AS than in TS and OS groups. Bacterial infections are significantly more frequent in children from the OS and AS groups, while fungal infections among TS children. Lymphopenia is the most common and most often underestimated SCID symptom. Almost 90% of children with TS and AS had lymphopenia before diagnosis, and SCID should be considered in all infants with lymphopenia, as it could have shortened DD. This is especially important if lymphopenia is accompanied by other cytopenia (e.g. AIHA) or dermatitis. High IgM concentration was observed in over ¼ of SCID patients. Further studies on larger groups are needed to clarify whether this could be a prognostic factor.

The most common gene variants causing SCID in our study were: *IL2RG* (23.8%), *RAG1/2* (16.6%), *JAK3* (14.3%), *ADA* (11.9%) and *IL7RA* (4.8%).

The survival rate was 69% in the presented group during the study period, with a lower rate in symptomatic than asymptomatic children – 67% and 83%, respectively – which confirms a better prognosis in case of earlier diagnosis.

It is extremely important to disseminate the awareness of SCID among pediatricians and other specialists, including hematologists, dermatologists and neonatologists. The milestone improving prognosis, survival and quality of life of both patients and families of that special group of inborn errors of immunity is to implement NBS for T-cell and B-cell lymphopenia in Poland.

DISCLOSURES

1. Institutional review board statement: The study was performed according to the Declaration of Helsinki Guideline on Biomedical Research Involving Human Subjects and was approved by the Bioethics Committee at the Children's Memorial Health Institute (Decision No. 30/KBE/2023).
2. Assistance with the article: We would like to express our gratitude to the Jeffrey Modell Foundation and the Department of Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands for providing access to genetic diagnostics. We are grateful to the patients and their parents for participating in the study.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

REFERENCES

1. Dvorak CC, Haddad E, Heimall J, Dunn E, Buckley RH, Kohn DB, et al. The diagnosis of severe combined immunodeficiency (SCID): The Primary Immune Deficiency Treatment Consortium (PIDTC) 2022 Definitions. J Allergy Clin Immunol 2023; 151: 539-546.
2. Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, et al. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. Blood 2011; 117: 3243-3246.
3. Piątosa B, Wolska-Kusnierz B, Siewiera K, Grzduk H, Gałkowska E, Bernatowska E. Distribution of leukocyte and lymphocyte subsets in peripheral blood. Age related normal values for preliminary evaluation of the immune status in Polish children. Centr Eur J Immunol 2010; 35: 168-175.
4. Abraham RS, Basu A, Heimall JR, Dunn E, Yip A, Kapadia M, et al. Relevance of lymphocyte proliferation to PHA in severe combined immunodeficiency (SCID) and T cell lymphopenia. Clin Immunol 2024; 261: 109942.
5. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy 2004; 59: 809-820.
6. Wolska-Kusnierz B, Pac M, Piatosa B, Pac, Kurenko-Deptuch M, Heropolitańska-Pliszka B, et al. Wartości referencyjne stężeń immunoglobulin G, A, M i D w surowicy zdrowych dzieci i osób dorosłych, mieszkańców województwa mazowieckiego. Standard Med Pediatr 2010; 3: 524-532.
7. Kreins AY, Dhalla, F, Flinn AM, Howley E, Ekwall O, Villa A, et al. European Society for Immunodeficiencies Clinical Working Party. European Society for Immunodeficiencies guidelines for the management of patients with congenital athymia. J Allergy Clin Immunol 2024; 18: S0091-6749(24)00980-1.
8. Bernatowska E, Wolska-Kuśnierz B, Pac M, Kurenko-Deptuch M, Pietrusza B, Zwolska Z, et al. Risk of BCG infection in primary immunodeficiency children. Proposal of diagnostic, prophylactic and therapeutic guidelines for disseminated BCG based on experience in the Department of Immunology, Children's Memorial Health Institute in Warsaw between 1980–2006. Centr Eur J Immunol 2007; 32: 221-225.
9. European Society for Immunodeficiences (ESID) Clinical Working Party Diagnostic Criteria for PID: BCG Diagnostic Criteria. Available from: https://archive.esid.org/Media/Files/BCG-diagnostic-criteria (accessed: 14.04.2025)
10. Sharapova SO, Skomska-Pawliszak M, Rodina YA, Wolska-Kuśnierz B, Dabrowska-Leonik N, Mikołuć B, et al. The clinical and genetic spectrum of 82 patients with RAG deficiency including a c.256_257delAA founder variant in Slavic countries. Front Immunol 2020; 11: 900.
11. Wolska-Kuśnierz B. Evaluation of treatment outcomes and immune system reconstitution in patients with primary immunodeficiencies following hematopoietic stem cell transplantation. Dissertation. The Children's Memorial Health Institute, Warsaw 2008.
12. Blom M, Soomann M, Soler-Palacín P, Šedivá A, Stray-Pedersen A, Zetterström R, et al. Newborn screening for SCID and severe T lymphocytopenia in Europe. J Allergy Clin Immunol 2024; 6: S0091-6749(24)01162-X.
13. Giżewska M, Durda K, Winter T, Ostrowska I, Ołtarzewski M, Klein J, et al. Newborn screening for SCID and other severe primary immunodeficiency in the Polish-German transborder area: experience from the first 14 months of collaboration. Front Immunol 2020; 11: 1948.
14. Mazalon M, Grześk E, Dąbrowska A, Urbańczyk A, Kołtan S. The significance of medical history and its impact on the early diagnosis of inborn error of immunity. Pediatr Pol 2024; 99: 246-249.
15. Lev A, Somech R, Somekh I. Newborn screening for severe combined immunodeficiency and inborn errors of immunity. Curr Opin Pediatr 2023; 35: 692-702.
16. Bernatowska E, Skomsa-Pawliszak M, Wolska-Kuśnierz B, Pac M, Heropolitanska-Pliszka E, Pietrucha B, et al. BCG moreau vaccine safety profile and NK cells-double protection against disseminated BCG infection in retrospective study of BCG vaccination in 52 Polish children with severe combined immunodeficiency. J Clin Immunol 2020; 40: 138-146.
17. Poyraz A, Cansever M, Muderris I, Patiroglu T. Neonatal lymphopenia screening is important for early diagnosis of severe combined immunodeficiency. Am J Perinatol 2023; 40: 748-752.
18. Delmonte OM, Villa A, Notarangelo LD. Immune dysregulation in patients with RAG deficiency and other forms of combined immune deficiency. Blood 2020; 135: 610-619.
19. Farmer JR, Foldvari Z, Ujhazi B, de Ravin SS, Chen K, Bleesing JJH, et al. Outcomes and treatment strategies for autoimmunity and hyperinflammation in patients with RAG deficiency. J Allergy Clin Immunol Pract 2019; 7: 1970-1985.e4.
20. Min Q, Csomos K, Li Y, Dong L, Hu Z, Meng X, et al. B cell abnormalities and autoantibody production in patients with partial RAG deficiency. Front Immunol 2023; 14: 1155380.
21. Vignesh P, Rawat A, Kumrah R, Singh A, Gummadi A, Sharma M, et al. Clinical, immunological, and molecular features of severe combined immune deficiency: a multi-institutional experience from India. Front Immunol 2021; 11: 619146.
22. Speckmann C, Nennstiel U, Hönig M, Albert MH, Ghosh S, Schuetz C, et al. Prospective newborn screening for SCID in Germany: a first Analysis by the Pediatric Immunology Working Group (API). J Clin Immunol 2023; 27: 1-14.
23. De Pagter AP, Bredius RG, Kuijpers TW, Tramper J, van der Burg M, van Montfrans J, et al. Overview of 15-year severe combined immunodeficiency in the Netherlands: towards newborn blood spot screening. Eur J Pediatr 2015; 174: 1183-1188.

24. Yao CM, Han XH, Zhang YD, Zhang H, Jin YY, Cao RM, et al. Clinical characteristics and genetic profiles of 44 patients with severe combined immunodeficiency (SCID): report from Shanghai, China (2004-2011). J Clin Immunol 2013; 33: 526-539.
25. Lee PP, Chan KW, Chen TX, Jiang LP, Wang XC, Zeng HS, et al. Molecular diagnosis of severe combined immunodeficiency – identification of IL2RG, JAK3, IL7R, DCLRE1C, RAG1, and RAG2 mutations in a cohort of Chinese and Southeast Asian children. J Clin Immunol 2011; 31: 281-296.
26. Al Sukaiti N, Ahmed K, Alshekaili J, Al Kindi M Cook MC, Al Farsi T. A decade experience on severe combined immunodeficiency phenotype in Oman, bridging to newborn screening. Front Immunol 2021; 11: 623199.
27. Abolhassani H, Chou J, Bainter W, Platt CD, Tavassoli M, Momen T, et al. Clinical, immunologic, and genetic spectrum of 696 patients with combined immunodeficiency. J Allergy Clin Immunol 2018; 141: 1450-1458.
28. Ikinciogullari A, Cagdas D, Dogu F, Tugrul T, Karasu G, Haskologlu S, et al. Turkish pediatric bone marrow transplantation sub group (TPBMT-SG). Clinical features and HSCT outcome for SCID in Turkey. J Clin Immunol 2019;39: 316-323.
29. Cirillo E, Cancrini C, Azzari C, Martino S, Martire B, Pession A, et al. Clinical, immunological, and molecular features of typical and atypical severe combined immunodeficiency: report of the Italian primary immunodeficiency network. Front Immunol 2019; 10: 1908.
30. Pasic S, Vujic D, Veljković D, Slavkovic B, Mostarica-Stojkovic M, Minic P, et al. Severe combined immunodeficiency in Serbia and Montenegro between years 1986 and 2010: a single-center experience. J Clin Immunol 2014; 34: 304-308.