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Original Article

Beyond Infections: Clinical and Genetic Spectrum of Pediatric Immune Dysregulation Disorders

Figen Çelebi Çelik, Aymen Hişmioğulları, Soner Günder, Gülçin Kaymakoğlu, Nesrin Gülez, Ferah Genel

University of Health Sciences Türkiye, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Department of Pediatrics, Division of Pediatric Allergy and Immunology, İzmir, Türkiye

ABSTRACT

Aim: Primary immune regulatory disorders represent a rapidly expanding subgroup of inborn errors of immunity. Unlike classical infection-predominant immunodeficiencies, these disorders may initially present with autoimmunity, lymphoproliferation, cytopenias, dermatologic disease, allergy, enteropathy, hemophagocytic lymphohistiocytosis, or malignancy.

Materials and Methods: We conducted a retrospective single-center observational cohort study of children with genetically confirmed diseases of immune dysregulation who had been followed at a tertiary pediatric immunology center between 2005 and 2025. Patients were included if their molecular diagnosis was classified under the International Union of Immunological Societies (IUIS) category of diseases of immune dysregulation. Demographic, clinical, genetic, therapeutic, transplant-related, and outcome data were extracted from the medical records and analyzed descriptively.

Results: Twenty-one children were included. Parental consanguinity was frequent (71.4%), and more than half of the cohort had a family history of primary immunodeficiency (57.1%). A substantial diagnostic delay was observed, with a median delay of 28 months (interquartile range, 8-105.5). The most common IUIS subcategory was regulatory T-cell defects (52.4%), followed by familial hemophagocytic lymphohistiocytosis syndromes with hypopigmentation (19.0%), autoimmune lymphoproliferative syndrome (14.3%), susceptibility to Epstein-Barr virus and lymphoproliferative conditions (9.5%), and immune dysregulation with colitis (4.8%). The main clinical features were lymphoproliferation (76.2%), hematologic abnormalities (66.7%) and autoimmunity (52.4%). Notably, malignancy was documented in 2 patients (9.5%). Antimicrobial prophylaxis was administered in 90.5% of the patients, immunoglobulin replacement in 66.7%, conventional immunosuppressive therapy in 38.1%, and biological or targeted therapy in 33.3%. Hematopoietic stem cell transplantation (HSCT) was performed in 8 patients (38.1%); immune reconstitution was achieved in all of the surviving transplant patients.

Conclusion: Pediatric diseases of immune dysregulation frequently present with non-infectious manifestations, particularly lymphoproliferation, cytopenias, autoimmunity, and dermatologic findings. Recognition beyond infection-centered warning signs, the integration of genetic testing, and the individualized use of targeted therapies or HSCT may improve care for this heterogeneous group of disorders.

Keywords: Primary immune regulatory disorders, diseases of immune dysregulation, inborn errors of immunity, autoimmunity, lymphoproliferation

Corresponding Author
Figen Çelebi Çelik, MD, University of Health Sciences Türkiye, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Department of Pediatrics, Division of Pediatric Allergy and Immunology, İzmir, Türkiye
E-mail: figencelebicelik@gmail.com **ORCID:** orcid.org/0000-0002-1100-4117
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Introduction

Inborn errors of immunity (IEIs) comprise a rapidly expanding group of monogenic disorders which affect immune development, immune function, and immune homeostasis. The most recent update from the International Union of Immunological Societies (IUIS) classified IEIs across multiple disease categories and reported 508 disease-associated genes and 17 phenocopies, highlighting the accelerating pace of gene discovery in this field (1). Within this evolving classification, diseases of immune dysregulation represent one of the most dynamic and clinically challenging IEI subgroups, encompassing defects which impair immune tolerance, lymphocyte apoptosis, regulatory T-cell function, cytotoxic lymphocyte activity, cytokine signaling, and host control of lymphoproliferation (1,2).

Primary immune regulatory disorders (PIRDs) are defined by impaired immune homeostasis rather than isolated susceptibilities to infection. In children, they may present with autoimmunity, autoinflammation, lymphoproliferation, enteropathy, endocrinopathy, severe allergic or dermatologic disease, hemophagocytic lymphohistiocytosis, or malignancy, with or without recurrent infections (2,3). Therefore, non-infectious findings such as autoimmune cytopenias, persistent lymphadenopathy or splenomegaly, early-onset enteropathy, severe eczema or allergy, or unexplained hematologic abnormalities should raise suspicion for an underlying monogenic immune regulatory defect (2-4).

The clinical recognition of PIRDs has expanded substantially with the growing use of next-generation sequencing, particularly whole-exome sequencing (WES), which is now widely integrated into the diagnostic work-up of those children with suspected IEI. Genomic testing has not only expanded the known mutational spectrum of immune dysregulation disorders, but it has also enabled earlier and more precise diagnosis in children with overlapping immune phenotypes (5). This is particularly important in highly consanguineous populations, where autosomal recessive immune dysregulation disorders may be enriched and affected children may present with severe, early-onset, multisystem disease (6). Despite this progress, diagnostic delay remains common, partly because the initial presentation may mimic hematologic, rheumatologic, gastroenterologic, dermatologic, allergic, or oncologic disorders rather than a classical primary immunodeficiency (1-4).

Management of PIRDs differs substantially from that of conventional infection-predominant immunodeficiencies. In addition to antimicrobial prophylaxis and immunoglobulin replacement, many patients require corticosteroids, steroid-sparing immunosuppressive agents, biologic therapies, or mechanism-based targeted treatments (2,7,8). In selected severe disorders, hematopoietic stem cell transplantation (HSCT) remains a potentially curative option, although transplant decisions require careful consideration of genotype, disease severity, organ damage, infection burden, and treatment response (7,8).

As PIRDs are rare and phenotypically heterogeneous, single center and registry-based pediatric cohorts remain valuable in defining real-world clinical patterns, diagnostic pathways, treatment requirements, and outcomes. Such studies are particularly important in increasing awareness regarding the consideration of immune dysregulation disorders. In this study, we aimed to describe the clinical, genetic, therapeutic, and outcome characteristics of children with genetically confirmed diseases of immune dysregulation who had been followed at a tertiary pediatric immunology center.

Materials and Methods

Study Design and Setting

This retrospective single-center observational cohort study was conducted at University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital. The medical records of those children diagnosed with genetically confirmed immune dysregulation disorders were retrospectively reviewed. This study aimed to evaluate the demographic characteristics, clinical presentation, genetic etiologies, disease course, treatment modalities, and outcomes of those children with immune dysregulation disorders. Ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval no.: 511, date: 11.02.2021). This study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design of this study, informed consent requirements were obtained according to institutional ethics committee regulations.

Study Population

The source population was identified retrospectively from the departmental records of those patients followed with suspected IEIs between 2005 and 2025. During this period, the records of 1,586 patients with suspected IEIs were reviewed. Among them, 265 patients had a genetically

confirmed diagnosis of IEIs. Of these genetically confirmed patients, 21 patients fulfilled the inclusion criteria by having a genetically confirmed IEI classified under the IUIS category of "Diseases of Immune Dysregulation" according to the IUIS Primary Immunodeficiency Diseases Committee Report on IEI (2024) classification and so they were included in the final analysis (1). Diagnoses were based on compatible clinical manifestations and molecular confirmation by genetic testing.

Patients were eligible for inclusion if they fulfilled all of the following criteria:

- Age below 18 years at symptom onset or diagnosis;
- A genetically confirmed diagnosis which was included in the IUIS category of Diseases of Immune Dysregulation;
- Clinical features compatible with immune dysregulation, such as autoimmunity, autoinflammation, lymphoproliferation, hemophagocytic lymphohistiocytosis, severe or recurrent infections, growth failure, dermatologic manifestations, or hematologic abnormalities;
- Availability of sufficient clinical follow-up data.

Patients were excluded if they had incomplete medical records preventing clinical classification or if molecular confirmation was unavailable. Patients with immune dysregulation-like clinical manifestations but without a genetically confirmed diagnosis within the IUIS Diseases of Immune Dysregulation category were not included in this study.

Data Collection

Data were retrospectively extracted from the hospital records and departmental follow-up files of the primary immunodeficiency patients followed up during the period 2005-2025. The following variables were recorded: sex, current age or age at death, age at first symptoms, age at diagnosis of primary immunodeficiency, diagnostic delay, parental consanguinity, family history of primary immunodeficiency, presenting symptoms, genetic diagnosis, clinical findings, complications, treatments, HSCT, and survival status.

Genetic Diagnosis

Genetic diagnoses were obtained from molecular testing results available in the patient records. The patients were categorized according to the affected gene and related immune pathway where applicable. The cohort included those patients with pathogenic or clinically relevant variants in genes associated with immune dysregulation. Genetic results were interpreted together with clinical and immunologic findings by pediatric immunology specialists.

Definitions of Clinical Manifestations

Lymphoproliferation was defined as the presence of persistent or recurrent splenomegaly, hepatomegaly, and/or pathological lymphadenopathy documented by physical examination and/or imaging. Hematologic manifestations included thrombocytopenia, immune thrombocytopenia, autoimmune hemolytic anemia, neutropenia, lymphopenia, or other clinically relevant cytopenias recorded during presentation or follow-up. Autoimmunity was defined as physician-diagnosed autoimmune disease, including autoimmune cytopenias, autoimmune endocrinopathy, or other organ-specific autoimmune manifestations. Infectious complications were defined as clinically significant infections, or those resulting in sequelae such as bronchiectasis; opportunistic, viral, fungal, and mycobacterial infections were also recorded. Immune reconstitution after HSCT was defined according to transplant follow-up records based on survival after transplantation with donor-derived hematopoietic recovery and sufficient immune recovery for routine outpatient follow-up.

Treatment Data

Treatment modalities were recorded for each patient. These included antimicrobial prophylaxis, immunoglobulin replacement therapy, conventional immunosuppressive therapy, biological or targeted agents, and HSCT. HSCT was recorded with the underlying diagnosis and survival status when available.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0. Categorical variables are summarized as frequencies and percentages, and continuous variables are reported as median and interquartile range (IQR). Percentages were calculated based on the available data for each variable. As this study was designed to describe the clinical, genetic, therapeutic, and outcome spectrum of genetically confirmed diseases of immune dysregulation, no comparative subgroup analysis or multivariable regression was performed.

Results

Demographic Characteristics of the Cohort

Of the 1,586 patients evaluated with suspected primary immunodeficiency, 265 had a genetically confirmed diagnosis. Among these, 21 patients fulfilled the IUIS criteria for "Diseases of Immune Dysregulation" and were included in the final cohort (Figure 1).

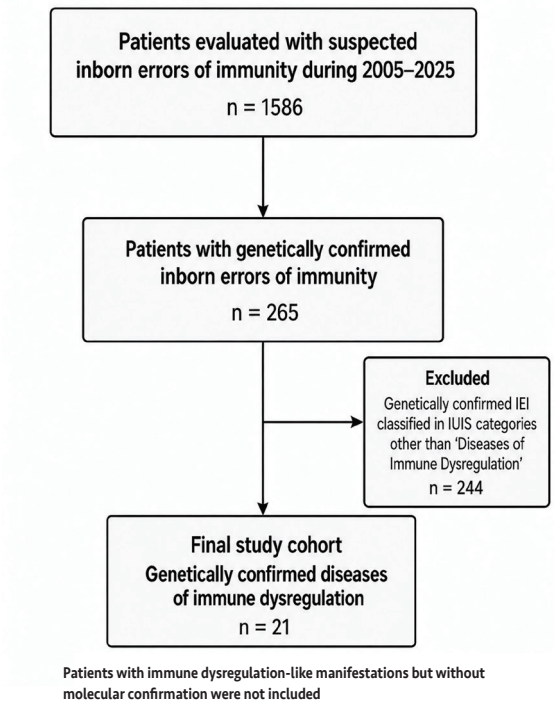

Figure 1. Patient selection flowchart

Of these, 10 patients were female (47.6%) and 11 were male (52.4%). Parental consanguinity was present in 15 patients (71.4%). A family history of primary immunodeficiency was documented in 12 patients (57.1%). Among the surviving patients, the median current age was 193 months (IQR, 134.25-257.5 months). The median age at first disease-related symptoms was 14 months (IQR, 2-49.5 months), whereas the median age at diagnosis of primary immunodeficiency was 91 months (IQR, 19.5-160.5 months). The median diagnostic delay was 28 months (IQR, 8-105.5 months). The median follow-up duration was 98 months (IQR, 63-138 months).

Distribution According to IUIS Diseases of Immune Dysregulation Subcategories

According to the IUIS classification, all patients had genetically confirmed disorders listed under "Diseases of Immune Dysregulation". The cohort represented five IUIS subcategories: familial hemophagocytic lymphohistiocytosis (FHL) syndromes with hypopigmentation, regulatory T-cell defects, immune dysregulation with colitis, autoimmune lymphoproliferative syndrome (ALPS), and susceptibility to Epstein-Barr virus (EBV) and lymphoproliferative conditions (Figure 2). The largest subgroup was regulatory T-cell defects, identified in 11 patients (52.4%). This group included LRBA deficiency in 5 patients, CTLA4 haploinsufficiency in 2 patients, FOXP3-related IPEX syndrome in 2 patients, and NBEAL2 deficiency in 2 patients. In the IUIS classification, *CTLA4, LRBA, FOXP3*, and *NBEAL2* are listed under the regulatory T-cell defect category. The second subgroup was FHL syndromes with hypopigmentation observed in 4 patients (19%). This subgroup included RAB27A deficiency/Griscelli syndrome type-2 in 2 patients, LYST deficiency/Chediak-Higashi syndrome in 1 patient, and AP3B1 deficiency/Hermansky-Pudlak syndrome type-2 in 1 patient. ALPS-related defects were present in 3 patients (14.3%). This subgroup included TNFRSF6/FAS-related ALPS in 2 patients and CASP10 deficiency in 1 patient. Immune dysregulation with colitis was represented by 1 patient (4.8%) with IL10RB deficiency. Finally, susceptibility to EBV and lymphoproliferative conditions was present in 2 patients (9.5%), both with TNFRSF9/CD137 deficiency.

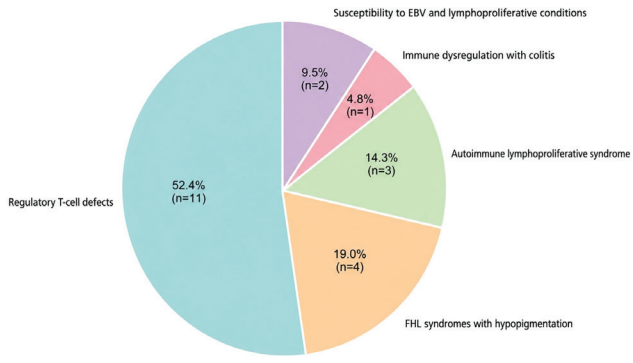

Figure 2. Distribution of patients according to IUIS diseases of immune dysregulation subcategories
EBV, Epstein-Barr virus, FHL: Familial hemophagocytic lymphohistiocytosis, IUIS: International Union of Immunological Societies

Clinical Manifestations at Diagnosis and During Follow-up

Lymphoproliferative manifestations were documented in 16 patients (76.2%). The recorded lymphoproliferative findings included splenomegaly in 16 patients (76.2%), hepatomegaly in 13 patients (61.9%), and pathological lymphadenopathy in 13 patients (61.9%); these findings were not mutually exclusive. Hematologic manifestations were observed in 14 patients (66.7%). At initial evaluation, thrombocytopenia was present in 7 patients (33.3%), 5 of whom had immune thrombocytopenia. During the entire disease course, thrombocytopenia was documented in 10 patients (47.6%), 7 of whom had immune thrombocytopenia. Other hematologic abnormalities included neutropenia in 5 patients (23.8%), autoimmune

hemolytic anemia in 5 patients (23.8%), and lymphopenia in 4 patients (19%). Autoimmunity was documented in 11 patients (52.4%), mainly autoimmune cytopenias in 9 patients (42.9%) and autoimmune endocrinopathies in 3 patients (14.3%). Recurrent sinopulmonary infections were present at diagnosis in 9 patients (42.9%). Dermatologic manifestations were observed in 7 patients (33.3%). Hypopigmented or silvery hair was present in 4 patients with cytotoxic trafficking defects, including 2 patients with RAB27A deficiency/Griscelli syndrome, 1 with Hermansky-Pudlak syndrome, and 1 with Chediak-Higashi syndrome. Eczematous skin involvement was documented in 2 patients with FOXP3/IPEX syndrome, and psoriasis was observed in 1 patient with CTLA4 haploinsufficiency. Allergic manifestations were recorded in 2 patients (9.5%), both with FOXP3/IPEX syndrome and food allergy. In addition, 2 patients (9.5%) were diagnosed through family screening because of previously identified primary immunodeficiencies in affected family members.

During follow-up, immune dysregulation-related and infectious complications were common and frequently involved multiple organ systems. Infection-related complications were observed in 7 patients (33.3%) during follow-up. Bronchiectasis was the most frequent infectious complication and was documented in 6 patients (28.6%) with CTLA4 haploinsufficiency, LRBA deficiency, TNFRSF6/FAS related disease, FOXP3/IPEX syndrome, IL10RB deficiency, and TNFRSF9/CD137 deficiency, and chronic lung disease was recorded in 1 patient with FOXP3/ IPEX syndrome. Abscess, pyoderma, or fungal skin infections occurred in 3 patients (14.3%) with CASP10, IL10RB, and LRBA deficiencies. Additional infectious complications included latent tuberculosis infection in 2 patients with LRBA deficiency, EBV disease in 1 patient with TNFRSF9/CD137 deficiency, and CMV infection in 1 patient with LRBA deficiency.

Hemophagocytic lymphohistiocytosis was recorded in 3 patients (14.3%), including patients with LYST deficiency and RAB27A/Griscelli syndrome.

Malignancy was recorded in 2 patients (9.5%). One patient with CASP10 deficiency developed lymphoma at 18 years of age, and one patient with TNFRSF9/CD137 deficiency developed EBV-associated B-cell lymphoma at 11 years of age. These findings indicate that, in this cohort, non-infectious manifestations, particularly lymphoproliferation, hematologic abnormalities and autoimmunity, were more frequent presenting features than infectious symptoms (Figure 3).

Therapeutic Management and Final Outcomes

Most patients required infection prophylaxis and/or immunomodulatory treatment during follow-up. Antimicrobial prophylaxis was used in 19 patients (90.5%), and immunoglobulin replacement therapy was administered to 14 patients (66.7%).

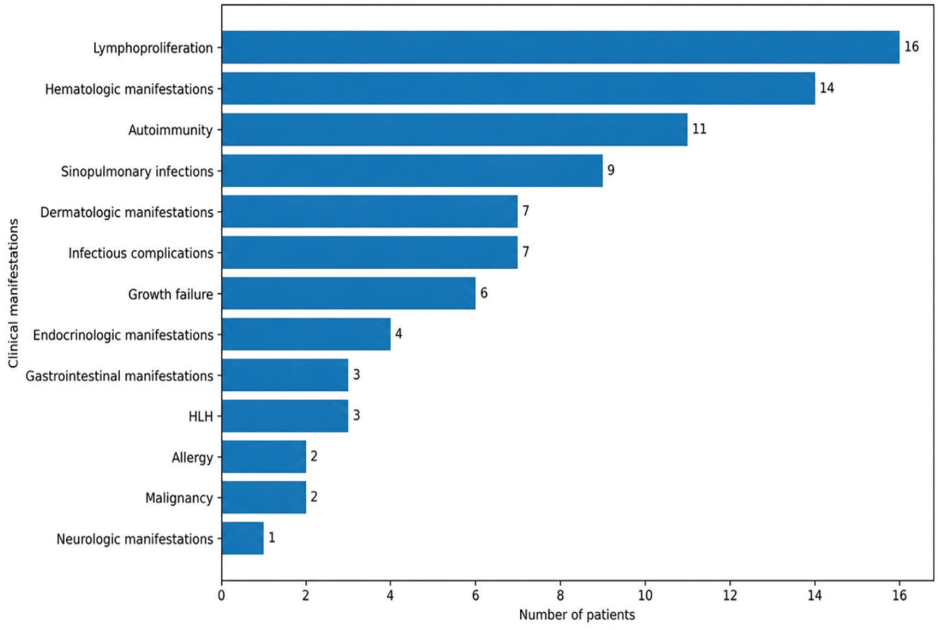

Figure 3. Presenting manifestations and immune dysregulation-related complications. The horizontal bar chart shows the frequency of major presenting manifestations and immune dysregulation-related complications in the study cohort
HLH: Hemophagocytic lymphohistiocytosis

Conventional immunosuppressive treatment was administered in 8 patients (38.1%). The recorded agents included systemic corticosteroids, cyclosporine, and sirolimus. Corticosteroids were mainly used for autoimmune cytopenias in patients with LRBA deficiency, TNFRSF6/FAS-related disease, TNFRSF9/CD137 deficiency, LYST deficiency/Chediak-Higashi syndrome, and CASP10 deficiency. Cyclosporine was used in one patient with TNFRSF9/CD137 deficiency, and sirolimus was used in one patient with CTLA4 haploinsufficiency. Biological agents were administered to 7 patients (33.3%). Abatacept was given to 6 patients, including 5 with LRBA deficiency and 1 with CTLA4 haploinsufficiency. In addition, 1 patient with TNFRSF9/CD137 deficiency received rituximab and bortezomib because of EBV-associated lymphoproliferation.

HSCT was performed in 8 patients (38.1%), including 2 patients with RAB27A deficiency/Griscelli syndrome, 2 with FOXP3/IPEX syndrome, and one each with LRBA deficiency, TNFRSF9/CD137 deficiency, LYST deficiency/Chediak-Higashi syndrome, and IL10RB deficiency. At the last follow-up, 5 of the 8 transplant patients (62.5%) were alive, all of whom had achieved immune reconstitution, while 3 had died. Deaths after HSCT occurred in patients with TNFRSF9/CD137 deficiency, LYST deficiency/Chediak-Higashi syndrome, and RAB27A deficiency/Griscelli syndrome. The patient with TNFRSF9/CD137 deficiency died due to septic shock.

At the last follow-up, 16 patients (76.2%) were alive, while 5 patients (23.8%) had died. The deceased patients had CTLA4 haploinsufficiency, LRBA deficiency, TNFRSF9/CD137 deficiency, LYST deficiency/Chediak-Higashi syndrome, and RAB27A deficiency/Griscelli syndrome. The median age at death was 68 months (IQR, 60-156 months). Comprehensive individual-level clinical, genetic, treatment-related, and outcome data for all of the patients are presented in Table I.

Table I. Clinical, genetic, therapeutic, and outcome characteristics stratified by IUIS diseases of immune dysregulation subcategories

No.	Genetic diagnosis/ disorder	Sex	Age at onset/ diagnosis, months	Clinical manifestations	Treatment	Outcome
FHL syndromes with hypopigmentation						
P10	RAB27A deficiency/ Griscelli syndrome type-2	M	12/22	Hypopigmented/silvery hair, hypothyroidism, hepatosplenomegaly, sinopulmonary infections, HLH	Antimicrobial prophylaxis, IVIG, HSCT	Alive; immune reconstitution after HSCT
P21	RAB27A deficiency/ Griscelli syndrome type-2	F	1/6	Hypopigmented/silvery hair, diarrhea, growth failure, HLH	Antimicrobial prophylaxis, IVIG, HSCT	Died after HSCT
P11	LYST deficiency/Chediak-Higashi syndrome	F	51/65	Hypopigmented/silvery hair, hepatosplenomegaly, neutropenia, thrombocytopenia, lymphopenia, sinopulmonary infections, HLH	Antimicrobial prophylaxis, corticosteroid, HSCT	Died after HSCT
P19	AP3B1 deficiency/ Hermansky-Pudlak syndrome type-2	M	1/7	Hypopigmented/silvery hair, sinopulmonary infections, growth failure, neutropenia, syndromic features, neuromotor retardation	Antimicrobial prophylaxis, IVIG	Alive
Regulatory T-cell defects						
P18	FOXP3 deficiency/IPEX syndrome	M	1/13	Eczema, growth failure, gastroenteritis, food allergy, chronic lung disease, bronchiectasis, eosinophilia	Antimicrobial prophylaxis, IVIG, HSCT	Alive; immune reconstitution after HSCT
P20	FOXP3 deficiency/IPEX syndrome	M	2/17	Eczema, growth failure, food allergy, eosinophilia	Antimicrobial prophylaxis, IVIG, HSCT	Alive; immune reconstitution after HSCT
P2	LRBA deficiency	F	6/199	Autoimmune hemolytic anemia, hepatosplenomegaly, lymphadenopathy, bronchiectasis	Antimicrobial prophylaxis, IVIG, abatacept	Died
P14	LRBA deficiency	M	12/82	Sinopulmonary infections, autoimmune hemolytic anemia, immune thrombocytopenia, splenomegaly, lymphadenopathy, latent tuberculosis infection	Antimicrobial prophylaxis, IVIG, corticosteroid, abatacept, HSCT	Alive; immune reconstitution after HSCT

Table I. Continued

No.	Genetic diagnosis/ disorder	Sex	Age at onset/ diagnosis, months	Clinical manifestations	Treatment	Outcome
P16	LRBA deficiency	M	14/185	Autoimmune hemolytic anemia, immune thrombocytopenia, chronic interstitial nephritis, splenomegaly	Antimicrobial prophylaxis, IVIG, corticosteroid, abatacept	Alive
P6	LRBA deficiency	F	3/107	Sinopulmonary infections, growth failure, Graves' disease, type 1 diabetes mellitus, hepatosplenomegaly, lymphadenopathy, CMV infection	Antimicrobial prophylaxis, IVIG, abatacept	Alive
P12	LRBA deficiency	M	2/40	Sinopulmonary infections, type 1 diabetes mellitus, Hashimoto thyroiditis, hepatosplenomegaly, lymphadenopathy, latent tuberculosis infection, pyoderma	Antimicrobial prophylaxis, IVIG, abatacept	Alive
P1	CTLA4 haploinsufficiency	F	48/54	Sinopulmonary infections, autoimmune hemolytic anemia, hepatosplenomegaly, lymphadenopathy	Antimicrobial prophylaxis, IVIG, abatacept	Died
P5	CTLA4 haploinsufficiency	M	24/130	Psoriasis, autoimmune hemolytic anemia, immune thrombocytopenia, hepatosplenomegaly, lymphadenopathy, bronchiectasis	Antimicrobial prophylaxis, IVIG, sirolimus	Alive
P7	NBEAL2 deficiency	M	70/129	ALPS-like disease, thrombocytopenia, hepatosplenomegaly, lymphadenopathy	Antimicrobial prophylaxis	Alive
P8	NBEAL2 deficiency	F	24/129	ALPS-like disease, thrombocytopenia, lymphopenia, hepatosplenomegaly, lymphadenopathy	Antimicrobial prophylaxis	Alive
Autoimmune lymphoproliferative syndrome						
P3	TNFRSF6/FAS-related ALPS	F	18/136	ALPS-like disease, immune thrombocytopenia, neutropenia, hypothyroidism, hepatosplenomegaly, lymphadenopathy, bronchiectasis	Antimicrobial prophylaxis, corticosteroid	Alive
P9	TNFRSF6/FAS-related ALPS	M	204/205	ALPS-like disease, immune thrombocytopenia, hepatosplenomegaly, lymphadenopathy	Antimicrobial prophylaxis, corticosteroid	Alive
P4	CASP10 deficiency	F	36/210	ALPS-like disease, neutropenia, immune thrombocytopenia, hepatosplenomegaly, lymphadenopathy, abscess, lymphoma	Corticosteroid, chemotherapy	Alive
Immune dysregulation with colitis						
P17	IL10RB deficiency	F	1/6	Sinopulmonary infections, growth failure, perianal abscess, rectovaginal fistula, colitis, bronchiectasis	Antimicrobial prophylaxis, IVIG, HSCT	Alive; immune reconstitution after HSCT
Susceptibility to EBV and lymphoproliferative conditions						
P15	TNFRSF9/CD137 deficiency	M	78/91	ALPS-like disease, immune thrombocytopenia, neutropenia, lymphopenia, splenomegaly, generalized lymphadenopathy, EBV-related B-cell lymphoma	Antimicrobial prophylaxis, IVIG, corticosteroid, cyclosporine, rituximab, bortezomib, chemotherapy, HSCT	Died after HSCT; due to septic shock
P13	TNFRSF9/CD137 deficiency	F	168/196	Sinopulmonary infections, hepatosplenomegaly, lymphopenia, lymphadenopathy, bronchiectasis	Denied treatment	Alive

ALPS: Autoimmune lymphoproliferative syndrome, CMV: Cytomegalovirus, EBV, Epstein-Barr virus, FHL: Familial hemophagocytic lymphohistiocytosis, HLH: Hemophagocytic lymphohistiocytosis, HSCT: Hematopoietic stem cell transplantation, IUIS: International Union of Immunological Societies, IVIG: Intravenous immunoglobulin

Discussion

In this single-center pediatric cohort, genetically confirmed diseases of immune dysregulation showed a broad and severe clinical spectrum, dominated by lymphoproliferation, hematologic manifestations, autoimmunity, and infection-related morbidity. The most frequent IUIS subcategory was regulatory T-cell defects, followed by FHL syndromes with hypopigmentation, autoimmune lymphoproliferative syndrome, immune dysregulation with colitis, and susceptibility to EBV and lymphoproliferative conditions. These findings support the argument that PIRDs are not merely infection-predominant immunodeficiencies, but also multisystem disorders in which failure of immune tolerance, abnormal lymphocyte activation, impaired apoptosis, defective cytotoxicity, and disturbed host–virus surveillance can shape the presenting phenotype (1-4).

The high rate of parental consanguinity in our cohort is consistent with the genetic architecture of IEI in populations where autosomal recessive disorders are enriched. In our series, consanguinity was present in 71.4% of the patients, and a family history of primary immunodeficiency was documented in more than half of the cohort. In the Turkish PIRD cohort reported by Aykut et al. (5), next-generation sequencing identified disease-causing variants across 15 PIRD genes, including several novel variants, further illustrating that PIRD cohorts from Türkiye and its neighboring regions may have a distinctive genetic burden related to consanguinity and founder effects. A recent national registry study from a highly consanguineous population reported parental consanguinity in 88.1% of pediatric PIRD cases and a family history of PIRDs in 45.7%, emphasizing the importance of family-based risk assessments in such settings (6).

Diagnostic delay remains a major challenge in PIRDs, largely because these disorders often present outside the classical infection-centered framework of primary immunodeficiency. In the national registry reported by Alajmi et al. (6), children with PIRDs were diagnosed relatively early, with a short median delay between symptom onset and diagnosis, probably reflecting registry-based ascertainment, high clinical awareness, and the predominance of severe early-onset phenotypes such as FHL-related disorders. However, our cohort suggests that children with broader immune dysregulation phenotypes may remain undiagnosed for a prolonged period, particularly when the initial presentation is dominated by hematologic, autoimmune, lymphoproliferative, dermatologic, allergic, or endocrine manifestations rather than recurrent infections. This observation is also consistent with the ESID Registry analysis of 16,486 patients with IEI which showed that non-infectious presentations are an important route to diagnosis and that relying exclusively on infection-centered warning signs would potentially miss a substantial proportion of these patients (9). Together, these data emphasize that the Jeffrey Modell warning signs, although useful for infection-predominant IEIs, are insufficient for detecting many PIRDs. Children with unexplained cytopenias, persistent lymphadenopathy or splenomegaly, early-onset autoimmunity, severe eczema or allergy, enteropathy, HLH-like inflammation, malignancy, or a positive family history should therefore be considered for early immunologic evaluation and WES-based genetic testing, even when their infection history is not striking (9-11).

The distribution of genetic diagnoses in our cohort showed that regulatory T-cell defects constituted the largest subgroup, including LRBA deficiency, CTLA4 haploinsufficiency, FOXP3/IPEX syndrome, and NBEAL2 deficiency. LRBA deficiency and CTLA4 haploinsufficiency are prototypic immune checkpoint disorders characterized by autoimmunity, lymphoproliferation, hypogammaglobulinemia, enteropathy, and recurrent infections (7,12,13). In line with previous reports showing that these disorders do not follow a uniform clinical pattern, our patients with LRBA deficiency and CTLA4 haploinsufficiency displayed overlapping CVID-like, ALPS-like, and autoimmune phenotypes (7,12,13). Although NBEAL2 deficiency has classically been recognized as the molecular cause of gray platelet syndrome, it is now classified among regulatory T-cell defects in the updated IUIS classification (1). A recent study showed reduced CTLA-4 expression in activated conventional T-cells from patients with NBEAL2 deficiency, providing a biological rationale for considering NBEAL2 deficiency as a CTLA-4 pathway-related immune dysregulation disorder (14).

Our cohort also illustrates the phenotypic diversity which may occur even within the same genotype or family. This was particularly evident in the siblings with TNFRSF9/CD137 deficiency. One sibling developed EBV-related B-cell lymphoma, required chemotherapy, rituximab, bortezomib, and HSCT, and died of septic shock after transplantation, whereas the other remains alive without disease-specific treatment. CD137 is critical for effective T-cell responses against EBV-infected cells, and TNFRSF9 deficiency has been associated with EBV-driven lymphoproliferation and lymphoma susceptibility (15,16). Such intrafamilial variability

is increasingly recognized in IEIs and may reflect differences in viral exposure, immune maturation, modifying variants, somatic events, treatment timing, or other environmental factors (17). This sibling pair highlights that genotype alone may not be sufficient to predict disease severity and that long-term surveillance is warranted even in apparently mildly affected relatives.

The therapeutic profile of our cohort underscores the high morbidity of pediatric PIRDs. Management often extended beyond infection prevention and immunoglobulin replacement to include immunosuppressive agents, pathway-directed biological therapies, and, in selected severe cases, HSCT. Previous studies have shown that abatacept can control autoimmune and inflammatory manifestations in LRBA deficiency and CTLA4 insufficiency, although treatment responses may be incomplete and long-term therapy does not eliminate all risks, including infection, progressive organ damage, or malignancy (12,14,18). While CTLA-4 pathway disorders provide a clear example of mechanism-based replacement therapy with abatacept, other PIRDs require different individualized approaches according to the dominant pathogenic mechanism. In one patient with TNFRSF9/CD137 deficiency, rituximab and bortezomib were administered for EBV-associated lymphoproliferation, reflecting the need for tailored treatment strategies in EBV-driven immune dysregulation.

HSCT was performed in selected patients with severe disease phenotypes. More than half of these transplant patients were alive at the last follow-up, and immune reconstitution was achieved in all of the surviving transplant patients. However, three deaths occurred after HSCT, underscoring that transplantation can be curative but remains high-risk in children with advanced immune dysregulation, active infection, HLH, or severe organ involvement. HSCT is generally considered the definitive therapy for selected disorders such as FOXP3/IPEX syndrome, IL10RB deficiency with severe early-onset colitis, Griscelli syndrome type-2, Chediak-Higashi syndrome, and other cytotoxicity or trafficking defects with HLH susceptibility (19-22). However, HSCT is not uniformly indicated for all PIRD categories. In ALPS-FAS, for example, medical treatment with corticosteroids, mycophenolate mofetil, or sirolimus is generally preferred for autoimmune cytopenias and lymphoproliferation, while HSCT is exceptional (23). For LRBA deficiency and CTLA4 haploinsufficiency, HSCT may prevent ongoing disease progression in selected patients, but the decision requires careful assessment of disease activity, organ damage, infection burden, and response to CTLA-4-Ig or other immunomodulatory therapies (13,18,24).

Malignancy development in patients with PIRDs may result from chronic immune activation, defective apoptosis, impaired tumor immune surveillance, persistent viral stimulation, or a combination of these mechanisms, depending on the underlying genetic defect (25). In our cohort, lymphoma developed in two patients: one with CASP10 deficiency at 18 years of age and one with TNFRSF9/CD137 deficiency who developed EBV-associated B-cell lymphoma at 11 years of age. ALPS-related apoptosis pathway defects have long been associated with lymphoproliferation and lymphoma risk, whereas TNFRSF9/CD137 deficiency illustrates how impaired EBV immune control may predispose to EBV-associated lymphoproliferative disease and lymphomagenesis (15,16,25). Therefore, the follow-up of patients with PIRDs should not be limited to infection control or the management of acute autoimmune manifestations, but should also include long-term surveillance for lymphoid malignancy, viral persistence, and progressive organ damage.

Study Limitations

The genetically confirmed diagnosis of all of the patients and their classification according to IUIS subcategories are among the main strengths of this study. The cohort provides real-world pediatric data from a tertiary immunology center in a population with a high rate of consanguinity and includes rare diagnoses such as NBEAL2 deficiency and TNFRSF9/CD137 deficiency. This study also reflects the therapeutic diversity of pediatric PIRDs, including conventional immunosuppression, CTLA-4-Ig therapy, anti-CD20/plasma cell- directed treatment, and HSCT. The retrospective design and the lack of standardized measures for disease activity, treatment response, and longitudinal organ involvement were the limitations of this study. The prospective use of tools such as IDDA2.1 scores can improve comparability among future PIRD cohorts (26). In addition, the absence of classical primary HLH genes such as *PRF1, UNC13D, STX11*, and *STXBP2* may reflect referral bias, as these patients are often diagnosed and managed primarily in pediatric hematology or transplant units. As pediatric diseases of immune dysregulation are rare and genetically heterogeneous, the number of patients included in this study was limited, which prevented robust subgroup comparisons, and the extended retrospective review period may have influenced case identification because diagnostic awareness, immunologic evaluation, and access to genetic testing improved over the study period.

Conclusion

In conclusion, this cohort shows that genetically confirmed pediatric diseases of immune dysregulation are characterized by early onset, substantial diagnostic delay, high consanguinity, frequent non-infectious manifestations, and a considerable need for advanced therapies. Lymphoproliferation, hematologic abnormalities, autoimmunity, dermatologic disease, HLH, and malignancy should prompt consideration of PIRDs, even when recurrent infections are not the dominant feature. Increasing awareness beyond infection-centered warning signs, integrating WES into the diagnostic pathway, and applying mechanism-based therapies or HSCT in carefully selected patients may improve outcomes in this expanding group of IEIs.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval no.: 511, date: 11.02.2021).

Informed Consent: Due to the retrospective design of this study, informed consent requirements were obtained according to institutional ethics committee regulations.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.Ç.Ç., N.G., F.G., Concept: F.Ç.Ç., A.H., Design: F.Ç.Ç., A.H., Data Collection or Processing: A.H., S.G., G.K., Analysis or Interpretation: F.Ç.Ç., A.H., Literature Search: F.Ç.Ç., A.H., Writing: F.Ç.Ç.

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