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RESEARCH ARTICLE

Evaluation of Patients with Severe Combined Immunodeficiency Due to Adenosine Deaminase Deficiency: A Single-Center Experience

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ABSTRACT

Objective: This study aimed to evaluate the clinical, immunological, and prognostic features of seven patients diagnosed with Adenosine Deaminase-Deficiency Severe Combined Immunodeficiency (ADA-SCID) at Marmara University. The aim of this study was to enhance the recognition and management of this condition, which is characterized by impaired lymphocyte development and early severe infections.

Methods: This retrospective study included seven patients with ADA-SCIDs who were monitored from 2012 to 2024. Patient data, including demographics, clinical findings, laboratory results, and imaging, were retrieved from hospital records. Diagnostic criteria focused on ADA enzyme activity and genetic mutations. Treatment regimens, such as immunoglobulin replacement, antimicrobial prophylaxis, enzyme replacement therapy, and hematopoietic stem cell transplantation (HSCT), were documented. Statistical analyses were performed using descriptive methods.

Results: The cohort (6 males, 1 female) presented a median age at diagnosis of 3 months. Consanguinity was observed in 86% of cases. Key symptoms included lymphopenia, recurrent infections, thymus absence, and systemic manifestations. Six patients received HSCT, and two underwent matched donor transplantation. One patient received gene therapy because of the absence of a matched donor. Opportunistic infections were prevalent, including cytomegalovirus and recurrent skin infections noted. Overall, two patients died of post-HSCT complications.

Conclusions: ADA-SCID is a life-threatening condition characterized by early severe infections and systemic manifestations. Early diagnosis and tailored treatment, including HSCT and gene therapy, are essential for improving survival outcomes. This study emphasizes the importance of early diagnosis to improve the survival and management outcomes of patients with ADA-SCID.

Keywords: Adenosine Deaminase Deficiency, Child, Hematopoietic Stem Cell Transplantation Inborn Errors of Immunity, Lymphopenia, Severe Combined İmmunodeficiency

INTRODUCTION

Adenosine deaminase (ADA) deficiency is a rare autosomal recessive disorder of purine metabolism [1]. Among patients with ADA deficiency, 80% presented with infantile severe combined immunodeficiency (SCID). Although the global incidence of this disease is unknown, it is estimated to occur in 1 in 200,000 live births [2]. ADA is a critical enzyme that is highly expressed in mammalian tissues, particularly the thymus and lymphoid cells. It converts adenosine (Ado) and deoxyadenosine to inosine and deoxyinosine in purine catabolism. Autosomal recessive defects in ADA lead to toxic accumulation of Ado and dAdo in cells, plasma, and tissues, impairing lymphocyte development and function. Thymic dysplasia and increased T-cell apoptosis are observed in patients with SCID, resulting in SCID symptoms with severe deficiency of T, B, and NK cells [1-3].

Approximately 80% of patients with ADA deficiency present with an early-onset severe combined immunodeficiency (ADA-SCID) phenotype, while 15-20% present with a less severe "delayed" or "late-onset" combined immunodeficiency (ADA-CID) phenotype in older children and adults. Patients with ADA-SCID typically experience recurrent, severe infections in the first months of

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life that, if left untreated, often result in death within 2 years. Cytomegalovirus infections, which can be acquired in utero through breastfeeding or blood transfusions, are of particular concern because these pathogens often cause irreversible organ damage [2]. Some patients with ADA deficiency present with Omenn syndrome, which is characterized by erythroderma, enterocolitis, lymphadenopathy, splenomegaly, and hepatic dysfunction [2]. Most patients with ADA deficiency also have a variety of systemic manifestations, including skeletal, brain, pulmonary, hepatic, and skin manifestations [3, 4]. Patients with ADA-CID deficiency may have fewer lymphoid systemic problems; these patients may have bronchiectasis, liver or bone marrow failure, autoimmune disease, or allergy [2]. Autoimmune manifestations include hypothyroidism and diabetes mellitus, hemolytic anemia, thrombocytopenia and neutropenia, and hepatitis [2].

Due to its high success and survival rates, hematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling donor (MSD) or family donor (MFD) is the preferred treatment option for ADA-SCID patients [2, 3, 5]. Another effective treatment option is ADA gene therapy using autologous hematopoietic stem cells. After the diagnosis of ADA-SCID, ADA enzyme replacement therapy conjugated with polyethylene glycol can be applied as a bridge therapy until the patient undergoes HSCT or gene therapy [2, 5].

Untreated patients with ADA-SCID may experience life-threatening opportunistic infections that can lead to irreversible organ failure and death from the first weeks of life. Early diagnosis and effective treatment management significantly increase the survival rate. Therefore, an early diagnosis and treatment access are crucial for patients with ADA-SCIDs. This study aimed to identify the clinical and laboratory characteristics of patients with SCID due to ADA deficiency to facilitate the recognition of the disease and to elucidate its natural course.

MATERIALS AND METHODS

Seven patients with ADA-SCID who were diagnosed and followed up at the Department of Pediatric Allergy and Immunology of Marmara University between 2012 and 2024 were included in our study. Demographic characteristics, clinical findings, laboratory results, follow-up time, and disease course of the patients were retrospectively evaluated. Data were obtained from patient records and the hospital's electronic system. This study was approved by the ethics committee of Marmara University (09.2019.511).

ADA enzyme activity (nmol/hr/mg) and deoxyadenosine nucleotide (dAXP) levels (mmol/L, %) were measured in dried blood extracts. ADA deficiency was defined as the absence of enzyme activity (<1%) in dried blood extracts or red blood cells and/or the detection of pathogenic biallelic or compound heterozygous variants in the ADA gene [1, 6].

Complete blood count, antibody responses to vaccine antigens, immunoglobulin levels before immunoglobulin replacement therapy, and immunophenotyping results by flow cytometry were evaluated [7]. The presence of documented viral infections and specific microorganisms growing in the culture were recorded. Radiographic images of the patients were evaluated, and the presence or absence of the thymus was noted.

Immunoglobulin replacement therapy, prophylactic treatments, enzyme replacement therapy, HSCT, and ADA gene therapy were recorded. Donor type, conditioning regimen, and post-HSCT complications were also evaluated.

Data Analysis

Statistical analyses were conducted using Xls and Jamovi 2.3.26 (The Jamovi Project, Australia) software [8]. Descriptive statistical methods such as median and minimum maximum were used in data analysis.

RESULTS

Patient Characteristics

The study included seven patients (6 Male, 1 Female), two of Syrian origins, and five of Turkish origins. The median age at diagnosis was 3 months (min-max: 1-14), with a median symptom onset of 1 month (min-max: 1-8) and a diagnostic delay of 2 months (min-max: 0-9 months). Consanguinity was present in six patients (86%), with no reported cases of inborn errors of immunity in the families. The most common presenting symptoms were moniliasis and diarrhea in four patients (57%) and lower respiratory tract infection (LRTI) in three patients (42%). None of the patients had tonsillar tissue. Radiographs showed the absence of the thymus in all patients (Figure 2a). At diagnosis, minor dysmorphic features were noted in P4 and P5 (low-set ears and a hooked nose in P4; coarse facial features in P5), along with hepatomegaly in P4, P5, and P7, and an erythematous eczematous rash in P1, P2, P3, and P7. P2 had multiple vesicular lesions around the right eye and nail dystrophy, while pes equinovarus was seen in P6 (Figure 2b). The detailed clinical features are shown in Table 1 and Figure 1.

Infection-related and non-infectious complications

From diagnosis to HSCT, the most common infection was LRTI in all patients, except for those with P2 and P4. P2 experienced recurrent skin infections. Opportunistic infections were observed in all patients except those at P6 and P7. Cytomegalovirus (CMV) viremia was detected in P1, P2, P3, and P4. HSV-associated conjunctivitis, keratitis, and skin infection were observed in P2. Sepsis by Acinetobacter baumannii was observed in P5. P1, P3, and P6 were vaccinated with attenuated live vaccine strains before diagnosis. P1 received the Bacillus Calmette-Guérin (BCG), oral polio, measles, mumps, rubella (MMR), and varicella vaccines, while P3 and P6 received the BCG vaccine. No vaccine-related complications were observed in any patient.

During the assessment of comorbidities, failure to thrive was observed in P1, P4, P5, and P7; chronic diarrhea in P1, P3, and P7; lymphoproliferation in P5; and bronchiectasis in P3. In addition, developmental delays in neuromotor milestones were

Table 1. Demographic and clinical features of patients

Patient ID	P1	P2	P3	P4	P5	P6	P7
Age at Presentation (month)	14	1	10	2	5	2	3
Sex	Female	Male	Male	Male	Male	Male	Male
Ethnicity	Syrian	Turkish	Turkish	Turkish	Turkish	Turkish	Syrian
Consanguinity	(+)	(+)	(-)	(+)	(+)	(+)	(+)
Clinical Findings							
Age at onset (month)	1	1	1	2	1	1	1
Presenting complaint	Chronic diarrhea Moniliasis Eczema	Skin infection	LRTI Chronic diarrhea Moniliasis	Moniliasis	LRTI	Moniliasis	LRTI Chronic diarrhea
Physical examination	Absent tonsils FTT BCG scar Eczema	Absent tonsils Eczema Vesicular lesions Nail dystrophy	Absent tonsils BCG scar Eczema	Absent tonsils FTT Atypical face HM	Absent tonsils FTT Atypical face HM	Absent tonsils BCG scar Pes equinovarus	Absent tonsils FTT HM Eczema
Clinical Follow-up	CMV viremia Pneumonia Chronic diarrhea Developmental delay	CMV viremia HSV keratitis Skin infections	CMV viremia Chronic diarrhea Bronchiectasis	CMV viremia	Brain abscess Hemiplegia LP	Pneumonia Ground-glass opacities	Atrial flutter Hypertension Chronic diarrhea
Treatment							
ERT	(-)	(+)	(+)	(+)	(+)	(+)	(+)
HSCT	(+)	(+)	(+)	(+)	(+)	(-)	(+)
GT	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Outcome	Alive	Deceased	Deceased	Alive	Alive	Alive	Alive
Genotype (ADA)	N/P	c.478+2T>C	c.452C>A, c.704G>A L152M, R235Q	c.245G>A R282Q	c.845G>A R282Q	c.478+2T>C	c.556G>A E186K

Abbreviations: ADA: adenosine deaminase, BCG: Bacillus Calmette–Guérin, CMV: Cytomegalovirus, ERT: Enzyme Replacement Therapy, FTT: Failure to Thrive, GT: Gene Therapy, HCST: Hematopoietic Stem Cell Transplantation, HM: Hepatomegaly, HSV: Herpes Simplex Virus, ID: Identification, LRTI: Lower Respiratory Tract Infection, LP: Lymphoproliferation, N/P: Not Performed, SCID: severe combined immunodeficiency

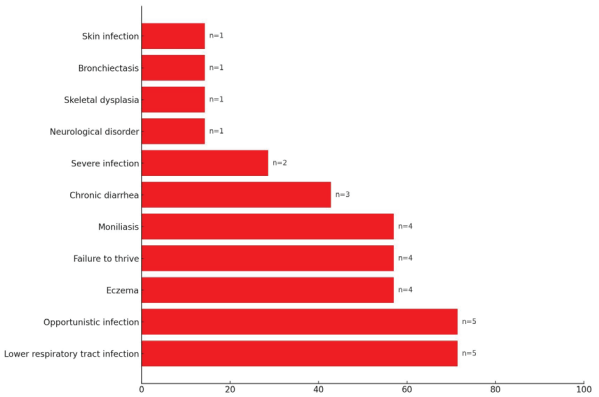

Figure 1: Distribution of the clinical findings of the patients.

noted at P1. A brain abscess was found on cranial magnetic resonance imaging (MRI) performed for left hemiplegia in P5. (Figure 2c). Sensorineural hearing loss was not observed in any of the patients. No autoimmune disease or malignancy was observed in any patient. Eczema was observed as an allergic manifestation in 4 patients. The detailed clinical features are shown in Table 1 and Figure 1.

Laboratory and Imaging Characteristics

Laboratory tests showed that all patients were lymphopenic at presentation (median, 100/mm^3 (min-max: 0-2600). While neutropenia was observed in P4, P6, and P7 (median: 3200/mm^3 (min-max: 200-7100), eosinophilia (840/mm^3 (min-max: 160-2560) was observed in P1, P2, P4, and P7. The median IgG levels were 369 mg/dL (min-max: 150-1152), IgA 22 mg/dL (min-max: 10-86) and IgM 15 mg/dL (min-max: 0-262). In the immunophenotyping performed by flow cytometry, the T–B–NK– SCID phenotype was identified in all patients, except for P3, who exhibited the T–B–NK+ SCID phenotype. Maternal engraftment was not detected in P6 and P7, for which results are available. ADA enzyme activity was <1% in all patients

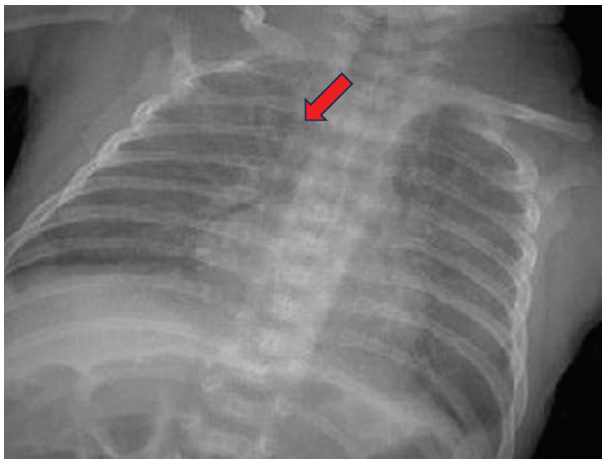

Figure 2a: X-ray image of P6 showing the absence of the thymus gland.

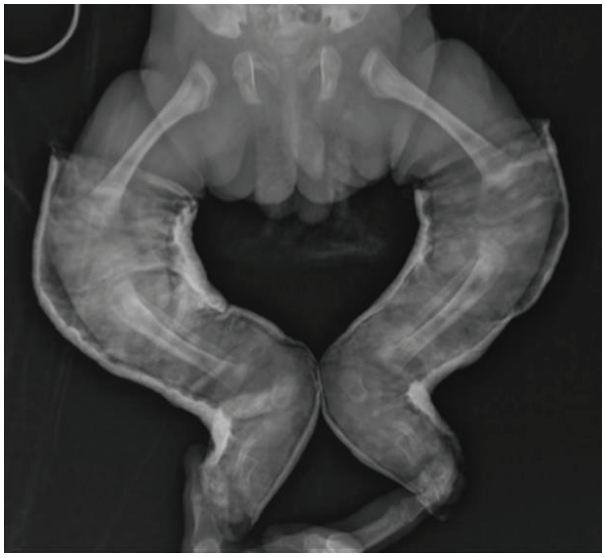

Figure 2b: X-ray image of P6 illustrating pes equinovarus.

(except P7, who was not tested) and dAXP levels exceeded 0.1 µmol/mL (or >2% of total) in all cases. The results are summarized in Table 2.

High-resolution computed tomography (HRCT) of the chest was performed at P3, P5, and P6 due to episodes of infection. P3 showed bronchiectasis, pleural thickening, and a tree-in-bud pattern, whereas P5 and P6 showed ground-glass opacities without evidence of bronchiectasis. At P5, a brain abscess was detected on cranial MRI, and subsequent imaging revealed cerebral atrophy. During P3's routine eye examination, MRI and MR angiography were performed on suspicion of papilledema and confirmed dilatation of the vein of Galen.

Genetic Characteristics

Five different variants were identified among the six families. Two patients (P2, P6) had a homozygous splice-site mutation, three (P4, P5, P7) had a homozygous missense mutation, and one patient (P3) had a compound heterozygous mutation (Table 1).

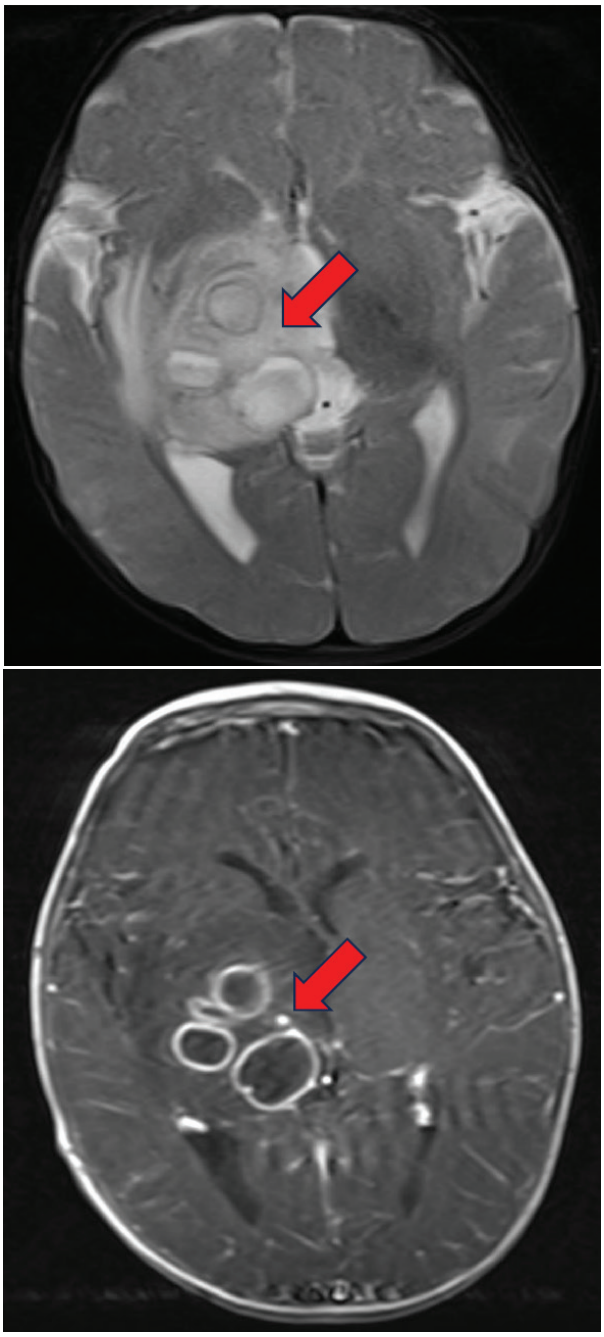

Figure 2c: Magnetic resonance imaging of P5 showing a brain abscess.

Treatments and Outcomes

All patients received immunoglobulin replacement and pathogen-specific antimicrobial prophylaxis. Six patients received polyethylene glycol conjugated ADA enzyme replacement therapy as bridge therapy for up to two weeks prior to HSCT for a median of 2.5 months (min-max: 1-10). Allogeneic hematopoietic stem cell transplantation (HSCT) was performed in six patients (86%): P1 and P3 received HSCT from a matched sibling donor, P2 and P5 from a matched family (non-sibling) donor, and P4 and P7 from a matched unrelated donor. P6 received autologous hematopoietic stem cell ADA

Table 2. Laboratory characteristics of the patients at the time of diagnosis

Patient ID	P1	P2	P3	P4	P5	P6	P7
White blood cell/mm³	5890	6400	11400	2300 (L)	8700	1600 (L)	2800 (L)
ANC/mm³	3200	3600	7100	200 (L)	6500	1100 (L)	1100 (L)
ALC/mm³	680 (L)	0 (L)	2600 (L)	100 (L)	100 (L)	100 (L)	200 (L)
AEC/mm³	1370 (H)	2560 (H)	300	1500 (H)	200	160	840 (H)
Platelet count/mm³	467000 (H)	524000 (H)	411000 (H)	361000	426000 (H)	554000 (H)	359000
IgG Level (mg/dL)	1152	552 (L)	369 (L)	415	152 (L)	275 (L)	150 (L)
IgM Level (mg/dL)	262 (H)	17 (L)	90	15 (L)	5 (L)	0 (L)	10 (L)
IgA Level (mg/dL)	86	22	43	22	21	12 (L)	10 (L)
IgE Level (mg/dL)	36	7	121 (H)	4 (L)	6 (L)	0 (L)	1 (L)
CD3+T cells/mm³	521 (L)	34 (L)	1694 (L)	5 (L)	24 (L)	35 (L)	13 (L)
CD3+4+T cells/mm³	250 (L)	16 (L)	1166	4 (L)	21 (L)	24 (L)	4 (L)
CD3+8+T cells/mm³	291 (L)	12 (L)	396 (L)	1 (L)	3 (L)	7 (L)	6 (L)
CD19+B cells/mm³	11 (L)	4 (L)	189 (L)	6 (L)	0 (L)	15 (L)	11 (L)
CD16+56+NK cells/mm³	105 (L)	62 (L)	215	30 (L)	1 (L)	10 (L)	49 (L)
RTE T cells (%)	6,8 (L)	-	9,5(L)	2 (L)	0,45 (L)	1,5 (L)	0
ADA Activity (nmol/hr/mg)	0	0	0	0	0	0	N/P
dAXP levels (%) (µmol/mL)	11 (H) -	14 (H) -	7 (H) -	48 (H) -	32 (H) -	- 3 (H)	- 25 (H)

Abbreviations: ADA: Adenosine Deaminase, AEC: Absolute Eosinophil Count, ALC: Absolute Lymphocyte Count, ALT: Alanine Aminotransferase, ANC: Absolute Neutrophil Count, AST: Aspartate Aminotransferase, dAXP: Deoxyadenosine Nucleotide, H: High, L: Low, Max: Maximum, Min: Minimum, NK: Natural Killer, RTE: Recent Thymic Emigrant.

gene therapy due to the lack of a fully matched donor. Patients were followed for a median of 34 months (min-max: 3-118), and two patients (29%) died due to post-HSCT complications. P2 died due to cranial GVHD after transplantation, but P3's cause of death could not be determined because post-transplantation follow-up was not continued in our clinic.

DISCUSSION

Severe combined immunodeficiency is a heterogeneous group of disorders caused by genetic defects that impair the development, function, and differentiation of T, B, and sometimes NK cells, resulting in deficiencies in cellular and humoral immune responses. Patients with SCID can be exposed to life-threatening infections in the first months of life [9]. Our ADA-SCID patients had severe infections such as persistent thrush, persistent eczema, recurrent pneumonia, and chronic diarrhea, as well as sepsis and cranial abscess, which typically occur after the first few weeks of life, indicating inborn errors of immunity (IEI). These are the red flags for the diagnosis of ADA-SCID. A history of consanguinity was found in 86% of the ADA-SCID patients. This is a high rate compared to the inbreeding rates reported in the literature [10], and we can say that this result reflects the high inbreeding rate in our region compared to Europe and America. Consanguinity and sibling loss due to IEI are other important indicators of IEI. The referral of patients with both recurrent infections and a history of consanguinity to immunologists should be prioritized [11].

In patients with SCID, opportunistic viral, bacterial, and fungal pathogens and live attenuated vaccines can lead to frequent and life-threatening infections [9,10]. Opportunistic infections were found in most patients (66%). In the Middle East and North Africa (MENA) region, live attenuated vaccines (e.g., BCG), which are widely administered in early infancy, are associated with high mortality rates among patients with IEI [10]. ADA-SCID is usually diagnosed in patients aged 3–12 months, and the median age at diagnosis in our patients was 3 months, which is consistent with the literature [1, 3]. In this context, early diagnosis of patients before live vaccination is critical. The T cell receptor excision circle (TREC) test is a sensitive diagnostic method for the early diagnosis of infants with SCID when used in newborn screening (NBS) [12]. NBS using the TREC test is widely used in the USA and worldwide [13] . However, it has not yet been introduced in Turkey. TREC test should be included in the NBS as soon as possible.

Adenosine deaminase is widely expressed in tissues. Therefore, the effects of ADA deficiency are not limited to the immune system; it also affects numerous organs and systems, including the lungs, liver, kidneys, skeletal system, skin, and nervous system [3, 14]. ADA deficiency is associated with a higher prevalence of non-infectious lung diseases, such as pulmonary alveolar proteinosis (PAP), compared with other genetic forms of SCID [14]. PAP results from surfactant phospholipid and apoprotein accumulation in the alveoli. Patients usually present within the first few weeks of life with respiratory distress, which may be accompanied by hypoxia and dyspnea. Characteristic findings include ground-glass opacities on lung imaging, while histopathologic examination shows granular periodic acid-

Schiff (PAS)-positive lipoprotein material and large, foamy macrophages containing PAS-positive material in the alveoli [2, 14, 15]. Ground glass opacities were observed on HRCT in two patients. One patient underwent bronchoscopy; however, histopathological examination did not reveal PAP. Chronic lung disease is a significant pulmonary problem in patients with ADA deficiency. Approximately 30% of these cases have chronic lung diseases, such as bronchiectasis, bronchiolitis obliterans, interstitial lung disease, and asthma. In our ADA cohort, one patient was found to have bronchiectasis associated with recurrent lung infection [1, 2].

ADA deficiency is characterized by marked skeletal abnormalities. Radiographic changes, such as costochondral cupping and scapular prominence, are observed in 50% of ADA-SCID patients at diagnosis. In patients with suspected congenital immune defects, radiographic findings may indicate ADA deficiency and aid in diagnosis [1, 16, 17]. Although these skeletal abnormalities were not observed, pes equinovarus was noted in one patient.

Individuals with ADA deficiency may experience a range of neurological and behavioral problems, from mild to severe. These include gross and fine motor impairments, seizures, sensorineural hearing loss, speech difficulties, attention deficit, hyperactivity, aggression, and social difficulties. The cognitive abilities of patients with ADA-SCID, as assessed by standardized intelligence tests, have been observed to be lower than those of age-matched controls, and this is thought to be related to increased levels of ADA expression in the brain [2, 14, 15, 18]. In our clinic, we routinely perform eye and hearing evaluations for all patients diagnosed with SCID. No hearing loss cases were observed among the ADA-SCID patient group. However, one patient had neuromotor delay and another had hemiplegia associated with a cranial abscess. Although ADA deficiency can present with various neurological symptoms, other potential neurological disorders should always be considered in the differential diagnosis. When evaluating the involvement of other organs and systems, liver involvement may be observed in individuals with ADA deficiency. Liver dysfunction is usually mild, and severe liver disease is rare [1, 15, 19]. However, abnormal liver function may appear as an early sign in individuals with ADA-SCID and should therefore be carefully evaluated [1]. In our ADA cohort, no clinically significant liver disease was observed although transient mild elevations in transaminase levels were noted in some patients during laboratory analysis. Our patients had skin involvement in the form of diffuse dermatitis, which is also common in other SCID patients. Dermatofibrosarcoma protuberans (DFSP), a rare malignant skin tumor with an increased frequency of ADA enzyme deficiency [1, 15], was not detected in any of our patients.

In patients with ADA-SCID, the initial hematologic finding is typically significant lymphopenia with a T–B–NK– immunophenotype. However, this finding is not specific to the disease, and patients may also present with T–B+NK+ or T–B–NK+ lymphocyte phenotypes [1, 2, 20]. In our study, six ADA-SCID patients exhibited the T–B–NK– SCID phenotype, while one patient exhibited the T–B–NK+ SCID phenotype. Pediatricians must be aware of lymphopenia to refer these patients to immunology clinics early to allow for prompt diagnosis and treatment. Neutropenia is another hematologic abnormality associated with ADA deficiency [1, 2, 14], and it was found in 43% of our patients. T-cell proliferation is either nonexistent or very poor in ADA-SCID patients, and a weak humoral response impairs both antibody synthesis and response to vaccination antigens. In our study, immunoglobulin levels were generally low for age, although two patients had normal IgG levels. ADA-SCID patients may have age-appropriate IgG levels during the first months of life because of maternal transfer via the placenta [1, 2]. In ADA deficiency, ADA enzyme activity is either absent or significantly reduced (<1%), with markedly elevated deoxyadenosine levels in erythrocytes [1-3, 6]. ADA enzyme activity was assessed in six of the patients, none of whom exhibited detectable activity. The deoxyadenosine nucleotide levels were evaluated in all patients and were elevated as expected. The absence of thymus tissue on imaging is a key finding in patients with ADA-SCID, serving as an early indicator of IEI and aiding in the evaluation of infants with suspected ADA-SCID [2]. X-ray imaging was performed in all patients, and none displayed thymus tissue.

HSCT is the preferred curative treatment for ADA-SCID patients. Additionally, ADA gene therapy and ERT are standard treatment options [1, 9, 11, 19]. In our center, the management of ADA-SCID patients begins, as with other SCID patients by ensuring isolation to reduce infection risks. To prevent opportunistic infections, antimicrobial prophylaxis with TMP-SMX, acyclovir, and fluconazole is administered, while antituberculosis prophylaxis with a combination of INH and RIF is initiated for patients who received the BCG vaccine. To prevent CMV infection, breastfeeding is continued if CMV infection is ruled out in the mother. IgRT treatment is started for all patients with SCID, regardless of serum antibody levels. The first step in planning curative treatment involves HLA typing of suitable family members to initiate a bone marrow transplant program, with ADA enzyme replacement as a bridging therapy until definitive treatment is available. Patients who lack suitable families or unrelated donors are directed toward gene therapy [1, 9-11].

In conclusion, untreated patients with ADA-SCID may experience life-threatening opportunistic infections, irreversible organ failure, and death from the first weeks of life. Early diagnosis and effective management can significantly increase the survival rate. Therefore, for the early recognition and treatment of ADA-SCID patients, red flags, including positive family history, early-onset severe or opportunistic infections, severe lymphopenia, and absence of the thymus on chest X-ray, are of great importance.

Ethics Committee Approval: This study was approved by the ethics committee of Marmara University (09.2019.511).

Informed Consent: Patients were retrospectively evaluated.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.B.E., S.B., E.K.A.; Data Acquisition- S.B., S.B.E., A.P.S., E.Y.G., R.A., S.C., N.K.Ö.; Data Analysis/Interpretation- A.O.Ö., S.B., M.Y.A., E.K.A., S.B.E.; Drafting Manuscript- S.B.E., S.B., R.A., N.K.Ö., A.P.S., E.Y.G., M.Y.A., S.C.; Critical Revision of Manuscript- A.O.Ö., E.K.A., S.B.; Final Approval and Accountability- S.B.E., S.B., A.P.S., E.Y.G., M.Y.A., S.C., R.A., N.K.Ö., S.B., A.O.Ö.E.K.A.

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