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Clinical and Immunological Characteristics of Adenosine Deaminase Deficiency in Early Infancy: A Single-Center Experience

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Abstract

Objective: Adenosine deaminase (ADA) deficiency is a rare inborn error of immunity caused by defects in purine metabolism and typically presents as severe combined immunodeficiency (ADA-SCID). The disease commonly manifests in early infancy with severe and recurrent infections. This study aimed to evaluate the clinical, immunological, biochemical, and genetic characteristics of patients diagnosed with ADA deficiency.

Methods: This retrospective study included patients with confirmed ADA deficiency who were followed in the Pediatric Allergy and Immunology Clinic between 2020 and 2026. Demographic characteristics, clinical findings, laboratory data, immunological parameters, metabolite analyses, genetic test results, treatment approaches, and clinical outcomes were reviewed.

Results: A total of six patients, including five males and one female, were included in the study. All patients were diagnosed within the first year of life, with a median age at diagnosis of 3.5 months (range, 1–7). Consanguinity was present in 83.3% of the patients. The most common presenting manifestation was recurrent pneumonia, observed in 66.7% of the patients. Oral candidiasis and chronic diarrhea were also frequently observed. Severe infectious complications occurred in 50% of the patients. Marked lymphopenia was present in all patients, with a median absolute lymphocyte count of 430/mm³ (range, 30–1570). Flow cytometric immunophenotyping demonstrated profound reductions in T-, B-, and NK-cell populations consistent with severe combined immunodeficiency. Biochemical analyses revealed markedly elevated dAXP levels in all patients, while adenosine levels were elevated in the majority of patients. Hematopoietic stem cell transplantation was performed in four patients, and five patients were alive at the last follow-up.

Conclusion: ADA deficiency is a life-threatening inborn error of immunity that should be considered in infants presenting with severe recurrent infections and profound lymphopenia. Early recognition of warning signs, including consanguinity and sibling death history, is essential for prompt diagnosis and timely therapeutic intervention to improve outcomes.

Keywords: Adenosine deaminase deficiency; severe combined immunodeficiency; ADA-SCID; lymphopenia; hematopoietic stem cell transplantation

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Erken Bebeklik Döneminde Adenozin Deaminaz Eksikliğinin Klinik ve İmmünolojik Özellikleri: Tek Merkez Deneyimi

Öz

Amaç: Adenozin deaminaz (ADA) eksikliği, pürin metabolizmasındaki bozukluklara bağlı gelişen ve tipik olarak ağır kombine immün yetmezlik (ADA-SCID) ile seyreden nadir bir doğuştan bağışıklık sistemi hastalığıdır. Hastalık sıklıkla erken bebeklik döneminde ağır ve tekrarlayan enfeksiyonlarla ortaya çıkar. Bu çalışmada, ADA eksikliği tanısı alan hastaların klinik, immünolojik, biyokimyasal ve genetik özelliklerinin değerlendirilmesi amaçlandı.

Yöntemler: Bu retrospektif çalışmaya 2020–2026 yılları arasında Pediatrik Alerji ve İmmünoloji Kliniği'nde takip edilen, doğrulanmış ADA eksikliği tanılı hastalar dahil edildi. Demografik özellikler, klinik bulgular, laboratuvar verileri, immünolojik parametreler, metabolit analizleri, genetik test sonuçları, tedavi yaklaşımları ve klinik sonuçlar değerlendirildi.

Bulgular: Çalışmaya beşi erkek, biri kız olmak üzere toplam altı hasta dahil edildi. Tüm hastalara yaşamın ilk yılı içinde tanı konuldu; tanı yaşı medyanı 3,5 ay (aralık, 1–7 ay) idi. Hastaların %83,3'ünde akraba evliliği mevcuttu. En sık başvuru bulgusu, hastaların %66,7'sinde görülen tekrarlayan pnömoniydi. Oral kandidiyazis ve kronik ishal de sık gözlenen klinik bulgular arasındaydı. Hastaların %50'sinde ciddi enfeksiyöz komplikasyonlar gelişti. Tüm hastalarda belirgin lenfopeni mevcuttu; mutlak lenfosit sayısı medyanı 430/mm³ (aralık, 30–1570) olarak saptandı. Akım sitometrik immünfenotipleme, ağır kombine immün yetmezlik ile uyumlu olarak T-, B- ve NK hücre popülasyonlarında belirgin azalma gösterdi. Biyokimyasal analizlerde tüm hastalarda belirgin yüksek dAXP düzeyleri saptanırken, adenozin düzeyleri hastaların çoğunluğunda yüksekti. Dört hastaya hematopoietik kök hücre nakli uygulandı ve son takipte beş hastanın hayatta olduğu görüldü.

Sonuç: ADA eksikliği, erken bebeklik döneminde ağır tekrarlayan enfeksiyonlar ve belirgin lenfopeni ile seyreden, yaşamı tehdit eden bir doğuştan bağışıklık sistemi hastalığıdır. Akraba evliliği ve kardeş ölüm öyküsü gibi uyarıcı klinik bulguların erken dönemde fark edilmesi, hızlı tanı konulması ve zamanında uygun tedavinin başlanması açısından büyük önem taşımaktadır.

Anahtar kelimeler: Adenozin deaminaz eksikliği, ağır kombine immün yetmezlik, ADA-SCID, lenfopeni, hematopoetik kök hücre nakli.

INTRODUCTION

Adenosine deaminase (ADA) deficiency is a rare inborn error of immunity caused by loss-of-function mutations in the ADA gene, leading to disruption of purine metabolism and resulting in severe combined immunodeficiency (SCID). The estimated incidence is approximately 1 in 200,000 live births. Clinically, nearly 80% of affected individuals present with early-onset severe combined immunodeficiency due to ADA deficiency (ADA-SCID), while a smaller proportion (15–20%) exhibit a milder, delayed-onset phenotype referred to as ADA-related combined immunodeficiency (ADA-CID), which may manifest later in childhood or adulthood[1,2].

The disease typically manifests in early life with severe infections and is characterized by profound impairment of both humoral and cellular immunity[1,2]. Clinically, it is associated with recurrent severe infections, persistent oral candidiasis, and opportunistic infections[3]. In addition to immunological manifestations, ADA deficiency has also been reported to cause non-infectious complications, including neurodevelopmental abnormalities and pulmonary involvement[8]. Various systemic manifestations involving the skeletal system, brain, lungs, liver, and skin have also been described in affected patients[4–6]. Although untreated ADA deficiency is associated with high mortality, survival rates have significantly improved with current therapeutic approaches, including hematopoietic stem cell transplantation and gene therapy[7].

ADA is a key enzyme in the purine degradation pathway and is essential for lymphocyte development and proliferation. Deficiency of

this enzyme leads to the accumulation of toxic purine metabolites, which induce apoptosis in lymphocytes and result in profound lymphopenia[3,8]. Consequently, ADA deficiency leads to a severe immunodeficiency affecting T, B, and NK cell functions. In recent years, increasing evidence has highlighted the phenotypic and genotypic heterogeneity associated with ADA deficiency[8]. In this study, we aimed to evaluate the clinical and immunological characteristics of patients diagnosed with ADA deficiency.

METHODS

This retrospective single-center study included patients with ADA deficiency who were followed at the Pediatric Allergy and Immunology Center between 2020 and 2026. Patients were eligible for inclusion if they had a confirmed diagnosis of ADA deficiency based on biochemical and/or molecular genetic evidence, together with clinical and immunological findings consistent with ADA-SCID. Patients with incomplete clinical data or without definitive diagnostic confirmation were excluded. The study was approved by the Ethics Committee of Dicle University Faculty of Medicine (Approval No. 2026/156).

Demographic characteristics (age and sex), presenting complaints, clinical findings, laboratory results, immunological parameters, metabolite analyses, genetic test results, treatment approaches, and clinical outcomes were retrospectively reviewed. Data were obtained from the hospital information management system and patient medical records.

Laboratory evaluations included complete blood count parameters and serum immunoglobulin levels (IgG, IgA, IgM). Lymphocyte subset distributions were determined by flow cytometry, and absolute T-, B-, and NK-cell counts were interpreted according to age-adjusted reference ranges.

The diagnosis of ADA deficiency was established based on clinical and immunological findings and confirmed by biochemical and/or molecular genetic analyses. Adenosine and deoxyadenosine nucleotide metabolite (dAXP) levels were measured from dried blood spot samples. ADA deficiency was defined by elevated dAXP levels in dried blood spot or erythrocyte samples and/or the identification of pathogenic biallelic or compound heterozygous variants in the ADA gene[1,9].

Statistical Analysis

Descriptive statistical analyses were performed. Continuous variables were expressed as median (minimum–maximum), while categorical variables were presented as frequencies and percentages.

RESULTS

Among the six patients included in the study, five were male and one was female. All patients were diagnosed within the first year of life, with a median age at diagnosis of 3.5 months (range, 1–7 months). Consanguinity was present in five of the six patients (83.3%). Two patients (P2 and P4) had a history of sibling death. However, no known family history of inborn errors of immunity was reported.

Most patients presented with severe infections early in life. Recurrent pneumonia was the most common presenting manifestation, observed in four of the six patients (66.7%). Gastrointestinal manifestations were also frequent, with diarrhea reported in four patients (66.7%), including chronic diarrhea in three patients (50%). Oral candidiasis was observed in three patients (50%). One patient was diagnosed through family screening following a history of sibling death, before the development of severe infections. Severe infectious complications were identified in three patients (50%), including CMV viremia and sepsis.

Physical examination revealed failure to thrive in three patients (50%), while absent tonsillar

tissue was observed in all patients. One patient (P1) exhibited minor dysmorphic facial features, including a flat nasal bridge and atypical facial appearance. None of the patients had lymphoproliferation or organomegaly, and no history of allergic disease or autoimmunity was identified. Four patients (66.7%) had received the BCG vaccine before diagnosis. Following diagnosis, infection prophylaxis was initiated in all patients. During follow-up, complications including chronic diarrhea, developmental delay, sepsis, CMV viremia, graft-versus-host disease, and post-transplant Hodgkin lymphoma were observed. The detailed clinical characteristics of the patients are presented in Table 1.

Table I: Demographic, Clinical, and Treatment Characteristics of Patients with ADA Deficiency

Characteristic	P1	P2	P3	P4	P5	P6
Sex	Male	Male	Female	Male	Male	Male
Age at symptom onset (months)	2	0	0	2	2	1
Age at diagnosis (months)	7	1	2	5	7	2
Follow-up duration (months)	39	36	12	1	10	2
Consanguinity	Yes	No	Yes	Yes	Yes	Yes
Sibling death history	No	Yes	No	Yes	No	No
Presenting symptoms	Recurrent pneumonia, diarrhea, oral candidiasis	Screening due to sibling death	Recurrent pneumonia, ecchymosis, oral candidiasis	Recurrent pneumonia, diarrhea	Recurrent pneumonia, diarrhea, oral candidiasis	Diarrhea and vomiting
Physical examination findings	Failure to thrive (<3rd percentile), dysmorphic facial features, flat nasal bridge, dark skin pigmentation, absent tonsils, BCG scar present	Weight and height 3–10th percentile, absent tonsils, no BCG scar	Weight and height 3–10th percentile, oral candidiasis, absent tonsils, dark skin pigmentation, no BCG scar	Failure to thrive (<3rd percentile), oral candidiasis, absent tonsils, BCG scar present	Failure to thrive (<3rd percentile), absent tonsils, oral candidiasis, BCG scar present	Weight and height at the 3rd percentile, absent tonsils, BCG scar present
Clinical course	Pneumonia, CMV viremia, chronic diarrhea, developmental delay, post-HSCT GVHD	Pneumonia, chronic diarrhea,	Pneumonia, post-HSCT GVHD, post-HSCT Hodgkin lymphoma	Pneumonia, sepsis	Pneumonia, developmental delay	Chronic diarrhea, CMV viremia
Prophylaxis	+	+	+	+	+	+
IgRT	+	+	+	+	+	+
ERT	+	+	+	–	+	+
HSCT	+	+	+	–	+	-
Gene therapy	–	–	–	–	–	-
Outcome	Alive	Alive	Alive	Deceased	Alive	Alive

Abbreviations: BCG, Bacillus Calmette–Guérin; CMV, Cytomegalovirus; GVHD, Graft-versus-host disease; HSCT, Hematopoietic stem cell transplantation; IgRT, Immunoglobulin replacement therapy; ERT, Enzyme replacement therapy

Laboratory Findings

Hematological evaluation revealed leukopenia in four of the six patients (66.7%). Marked lymphopenia according to age-adjusted reference values was present in all patients, with a median absolute lymphocyte count of $430/mm^3$ (range, 30–1570). Hemoglobin levels varied among the patients, and anemia was observed in four patients. Platelet counts were generally within the normal range, although thrombocytopenia was detected in one patient

(P4). Absolute neutrophil counts were within the normal range in all patients.

Serum immunoglobulin levels showed a heterogeneous distribution. The median serum IgG level was 378 mg/dL (range, 173–1015), the median IgM level was 28 mg/dL (range, 2–192), and the median IgA level was 25.5 mg/dL (range, 0–74). IgG and IgA levels were reduced in some patients, while IgM levels demonstrated considerable interpatient variability. Total IgE levels were low or within normal limits in all patients.

Flow cytometric immunophenotyping demonstrated profound T-, B-, and NK-cell lymphopenia in all patients, consistent with the immunophenotypic profile of severe combined immunodeficiency. However, the severity of cellular immunodeficiency varied among patients. Notably, substantial differences in absolute T-cell counts were observed even among patients harboring the same genetic variant. Laboratory findings at the time of diagnosis are summarized in Table 2.

Table II: Immunological and Hematological Findings at Diagnosis

	P1	P2	P3	P4	P5	P6
White blood cells (/mm³)	3810 ↓	2090 ↓	6030	2080 ↓	2750 ↓	5940
ANC (/mm³)	1350	1250	3420	1050	1710	3870
ALC (/mm³)	1570 ↓	90 ↓	480 ↓	30 ↓	380 ↓	970 ↓
HGB (g/dL)	10.7 ↓	14.8	13.6	9.4 ↓	9.2 ↓	8.7 ↓
Platelet count (/mm³)	203000	179000	275000	123000 ↓	388000	278000
IgG (mg/dL)	561	173 ↓	265 ↓	312	1015	444
IgM (mg/dL)	38 ↓	2 ↓	2 ↓	18 ↓	192	37
IgA (mg/dL)	28	0 ↓	1 ↓	23	56	74
Total IgE (IU/mL)	17	13	12	29	19	19
CD3+ T cells (/mm³)	779 ↓	3 ↓	152 ↓	2 ↓	20 ↓	843 ↓
CD3+CD4+ T cells (/mm³)	141 ↓	10 ↓	102 ↓	12 ↓	5 ↓	114 ↓
CD3+CD8+ T cells (/mm³)	587 ↓	25 ↓	85 ↓	5 ↓	201 ↓	517 ↓
CD19+ B cells (/mm³)	8 ↓	3 ↓	9 ↓	0.6 ↓	1.5 ↓	47 ↓
CD16+56+ NK cells (/mm³)	29 ↓	26 ↓	3 ↓	2 ↓	32 ↓	19 ↓

Abbreviations: ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, HGB: Hemoglobin, Ig: Immunoglobulin, NK: Natural killer, ↓: Below age-adjusted reference range

Adenosine and dAXP levels were assessed in all patients. Markedly elevated dAXP levels, exceeding the reference threshold of 0.1 µmol/L in all cases, demonstrated the characteristic biochemical profile of ADA deficiency. Adenosine levels were elevated in four of the six patients, while two patients had values within the reference range. The biochemical and genetic findings are summarized in Table 3.

Table III: Purine Metabolite Levels and Genetic Findings in Patients with ADA Deficiency

	P1	P2	P3	P4	P5	P6
Adenosine (µmol/L) *(reference 0.10–2.00)*	0.70	23.52 ↑	15.19 ↑	0.46	3.64 ↑	9,98↑
dAXP (µmol/L) *(reference <0.10)*	3.70 ↑	2.07 ↑	22.37 ↑	3.40 ↑	3.76 ↑	7.30↑
Genetic findings	c.302G>A (p.R101Q), homozygous	Genetic test result unavailable	c.678+1G>T, homozygous	c.302G>A (p.R101Q), homozygous	c.302G>A (p.R101Q) homozygous	c.302G>A (p.R101Q), homozygous

Abbreviations: dAXP: Deoxyadenosine nucleotides, ↑: Above reference range

Genetic analysis identified two different ADA variants. The c.302G>A (p.R101Q) missense variant was detected in four patients (P1, P4, P5, and P6), whereas the splice-site variant

c.678+1G>T was identified in one patient (P3). All detected variants were present in the homozygous state. No pathogenic variant was identified in one patient (P2) despite biochemical findings consistent with ADA deficiency.

Following diagnosis, infection prophylaxis and immunoglobulin replacement therapy were initiated in all patients. Enzyme replacement therapy was administered in five patients, and hematopoietic stem cell transplantation (HSCT) was performed in four patients. During post-transplant follow-up, graft-versus-host disease developed in two patients (P1 and P3), and one patient (P3) developed Hodgkin lymphoma during follow-up. One patient (P4), who did not undergo transplantation, died due to infectious complications. At the last follow-up, five patients were alive (Table 1).

DISCUSSION

In this study, we evaluated the clinical, immunological, biochemical, and genetic characteristics of patients diagnosed with ADA deficiency during early infancy. All patients were diagnosed within the first year of life, consistent with the classical early-onset ADA-SCID phenotype. Previous studies have shown that approximately 80% of patients with ADA deficiency present with severe combined immunodeficiency during early infancy, which is consistent with our findings[10,11].

In our cohort, recurrent pneumonia was the most common presenting manifestation, underscoring the predominance of lower respiratory tract infections in ADA-SCID. This finding is consistent with previous reports indicating that recurrent and severe respiratory infections are among the earliest and most prominent clinical manifestations of SCID[12–14]. Additionally, mucocutaneous candidiasis and gastrointestinal manifestations, including chronic diarrhea, were frequently observed, further reflecting the well-recognized clinical spectrum of combined immunodeficiency disorders.

A notable finding in our study was the high rate of consanguinity (83.3%), underscoring the importance of autosomal recessive inborn errors of immunity in our population. Similarly, a history of sibling death in two patients represented an important clinical clue for early diagnosis. These findings are particularly relevant in countries where newborn screening programs for SCID are not routinely implemented, emphasizing the need for heightened clinical awareness and prompt recognition[15].

Opportunistic viral, bacterial, and fungal pathogens may cause severe infections in patients with SCID[9,10]. In our cohort, severe infectious complications were observed in three of the six patients (50%). Live attenuated vaccines may lead to serious complications in individuals with inborn errors of immunity. In our study, four patients (66.7%) had received the BCG vaccine before diagnosis. The median age at diagnosis [3.5 months (range, 1–7)] indicates that some patients were exposed to live attenuated vaccines as part of routine immunization programs before the diagnosis of immunodeficiency was established. This observation further underscores the importance of early diagnosis, as live vaccines may result in severe infectious complications in patients with SCID[16].

Immunologically, all patients demonstrated marked lymphopenia with profound reductions in T-, B-, and NK-cell populations, consistent with severe combined immunodeficiency. ADA deficiency leads to the accumulation of toxic purine metabolites, which impair lymphocyte development and induce apoptosis, resulting in profound cellular immunodeficiency[17,18]. Despite this, serum immunoglobulin levels showed considerable variability among patients. This heterogeneity may be partly explained by the presence of maternally derived

immunoglobulins during early infancy, as previously reported[18,19].

Biochemically, markedly elevated dAXP levels were detected in all patients, supporting the diagnosis of ADA deficiency, while adenosine levels were elevated in the majority of patients. Metabolite analysis plays a crucial role in confirming the diagnosis and should be considered an essential component of the diagnostic work-up[17,20].

Although neurological and skeletal abnormalities have been reported in patients with ADA deficiency, such manifestations were less prominent in our cohort. While developmental delay was observed in some patients and one patient exhibited dysmorphic facial features, the broader spectrum of non-immunological manifestations described in previous studies was not evident. This variability likely reflects the marked phenotypic heterogeneity of ADA deficiency[20,21].

From a therapeutic perspective, HSCT remains the cornerstone of curative treatment for ADA-SCID. In our cohort, four patients underwent HSCT, although post-transplant complications, including graft-versus-host disease, were observed, reflecting the complexity of long-term management. One patient who did not undergo definitive transplantation died due to infectious complications, underscoring the critical importance of timely diagnosis and treatment. In addition to HSCT, ERT and gene therapy represent important therapeutic alternatives, particularly for patients who are not immediate candidates for transplantation[22–24].

This study has several limitations, primarily its retrospective single-center design and small sample size, which may restrict the generalizability of our findings. Nevertheless, given the rarity of ADA deficiency, such case series provide important real-world insights into its clinical presentation, diagnostic challenges, and therapeutic management.

In conclusion, ADA deficiency is a rare but severe inborn error of immunity that typically presents in early infancy with recurrent infections and profound lymphopenia. Our findings emphasize that early-onset severe infections, marked lymphopenia, consanguinity, and a history of sibling death may serve as important clinical warning signs. Early recognition and timely referral to specialized immunology centers are essential to facilitate prompt diagnosis and appropriate therapeutic intervention, thereby improving survival and long-term outcomes.

Ethics Committee Approval: The study was approved by the Ethics Committee of Dicle University Faculty of Medicine (Approval No. 2026/156).

Conflict of Interest: The author(s) declare that there is no financial conflict of interest related to this article.

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