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RESEARCH ARTICLE/ARAŞTIRMA

Severe Combined Immunodeficiencies Resulting from Impaired Purine Metabolism: Single Center Experience

Pürin Metabolizması Bozukluklarına Bağlı Ortaya Çıkan Ağır Kombine İmmün Yetmezlikler: Tek Merkez Deneyimi

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ABSTRACT

Objective: Deficiency of the purine salvage enzymes adenosine deaminase (ADA) or purine nucleoside phosphorylase (PNP) leads to severe combined immune deficiency (SCID). Since these enzymes are found in all cells, other tissues and organs are also affected, though more variably.

Materials and Methods: Here we describe the clinical course and treatment of one PNP deficient and 4 ADA deficient patients who were diagnosed in infancy. All had very low T-cell count and immunoglobulins, consistent with T-B-NK- SCID.

Results: Hematopoietic stem cell transplantation (HSCT) was performed in two patients with ADA deficiency. The ADA deficient patient who was treated with haploidentical HSCT (haplo-HSCT) died due to complications of HSCT. One of the ADA deficient patients died before HSCT and another ADA deficient patient is currently being treated with enzyme replacement treatment (ERT). The PNP deficient patient was treated with unrelated cord blood HSCT.

Conclusion: With this study, it was highlighted once again that the deficiency of purine salvage enzymes is important subgroup of SCIDs in Turkey.

Key words: ADA enzyme, PNP enzyme, purine salvage pathway, SCID

ÖZ

Giriş: Purin salvage yolağında bulunan adenozin deaminaz (ADA) ve purin nükleozid fosforilaz (PNP) enzim eksikliklerinde ağır kombine immün yetmezlik (AKİY) tabloları ortaya çıkabilmektedir. Bu enzimler tüm dokularda bulunur ve eksikliklerinde ortaya çıkan AKİY durumlarında farklı organlarda değişik derecelerde doku hasarları görülebilmektedir.

Gereç ve Yöntem: Makalede biri PNP ve dördü ADA eksikliğine bağlı süt çocukluğu döneminde tanı almış AKİY olgularımızın klinik seyir ve tedavileri sunulmuştur. Hastaların tamamı T-B-NK- AKİY fenotipi gösteriyordu ve hepsinin immünoglobulin değerleri düşüktü.

Bulgular: ADA eksiliğine bağlı AKİY olgularından ikisine kemik iliği transplantasyonu (KİT) yapıldı. Birine tam uyumlu kardeşten diğerine ise anneden haplo nakil gerçekleştirildi. Haplo nakil olan hasta KİT komplikasyonuna bağlı olarak, üçüncü ADA eksikliği hastası ise nakil beklerken kaybedildi. Bir diğer ADA eksikliği olan hasta halen enzim replasman tedavisi almaktadır. PNP eksikliği olan hasta ise yurtdışında kordon kanı transplantasyonu oldu.

Sonuç: Bu çalışma ile Türkiye'de pürin salvage yolak enzim eksikliklerine bağlı olguların AKİY'ler içinde önemli bir grubu oluşturduğu bir kez daha vurgulanmıştır.

Anahtar kelimeler: ADA enzim, PNP enzim, purin salvage yolağı, SCID

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INTRODUCTION

Adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) are sequential enzymes in the purine salvage pathway. ADA catalyzes the irreversible conversion of adenosine and 2'-deoxyadenosine (d-ADO) into the non-toxic nucleosides inosine and 2'-deoxyinosine, respectively. Next, PNP catalyzes the freely reversible conversion of inosine and guanosine into deoxyinosine and deoxyguanosine (d-GUO), respectively. The lack of ADA and PNP enzymes results in the accumulation of d-ADO and d-GUO in both intracellular and extracellular environments, and in the toxic intracellular accumulation of their nucleotide derivatives dATP and dGTP in lymphoid cells (1). The primary phenotype associated with inherited deficiency of ADA is profound lymphocyte depletion, resulting in T-B-NK-SCID characterized by recurrent severe opportunistic infections and failure to thrive which is usually diagnosed in the first months of life (2). PNP deficiency, which is more rare than ADA deficiency, is associated with low T-cell counts and function, and variable B cell dysfunction. In addition to recurrent infections, PNP deficient patients frequently manifest significant though variable neurologic dysfunction and autoimmunity (3). Both of these rare disorders have devastating consequences if they are not diagnosed and treated in a timely manner. Here we describe the clinical course of 4 ADA deficient patients who were diagnosed at from 4 weeks to 6 months of age, and one PNP deficient patient diagnosed at age 12 months. In this study, 3 patients (2 with ADA deficiency and 1 with PNP deficiency) underwent HSCT. The third ADA deficient patient died before HSCT and the fourth ADA deficient patient is currently being treated with enzyme replacement treatment.

CASES

Cases 1-4 Associated with ADA Deficiency

Case 1

A two-month-old boy was referred with a 15-day history of pneumonia. The family had previously lost a male child at 7 months of age due to SCID (genetic etiology not determined). The patient had profound lymphopenia and markedly decreased immunoglobulins, consistent with T-B-NK-SCID. The serum uric acid level was also low. In extracts of dried blood spots, PNP activity was normal but ADA enzyme activity was not detected. Genetic testing revealed a homozygous nonsense mutation (c.736C>T, p.Q246X) in exon 8 of the ADA gene (Table I). Antimicrobial prophylaxis [trimethoprim-sulfamethoxazole (TMP-SMX) and fluconazole], monthly intravenous immunoglobulin (IVIG) replacement, and ERT were started as treatment. ERT was administered for 4 week with a relatively good response. Absolute lymphocyte count (ALC) increased up to 800-1000/mm^3. A matched related donor could not be found, and his family accepted haplo-HSCT from the mother. This was performed at 4 months of age. Anti-thymocyte globulin (ATG, 10 mg/kg/day, 3 days) and cyclosporine were administered to the patient prior to HSCT for graft-versus-host disease (GvHD) prophylaxis. Also, rituximab (375 mg/m^2, one day) was administered prior to HSCT for EBV-associated post-transplant lymphoproliferative disease. In his follow-up, the patient suffered cytomegalovirus and *Candida albicans* infections and severe cutaneous and gastrointestinal GvHD (Grade 3). He died because of sepsis and GvHD at 8 months of age (Table II) (4).

Case 2

A 2-month-old girl was admitted with oral thrush and a positive family history for SCID (genetic etiology not determined). Physical examination revealed normal growth and oral thrush. Immunologic evaluation revealed profound lymphopenia,low immunoglobulins and low uric acid levels. The analysis of lymphocyte subsets indicated T-B-NK-SCID (Table I). The patient had a homozygous nonsense mutation (c.736C>T, p.Q246) in exon 8 of the ADA gene. ERT and antimicrobial prophylaxis with TMP-SMX and fluconazole, and monthly IVIG replacement were started as treatment. At 4 months of age, she underwent HSCT from a matched sibling donor (MSD). GVHD prophylaxis with ATG (10 mg/kg/day, 3 days) was used prior to the HSCT. The patient is 9 months old and alive in good condition. She does not need IVIG.

Case 3

A one-month-old girl was admitted with a history of an ADA-deficient cousin (Case 1). A diagnosis of SCID was made in the asymptomatic period. Immunologic evaluation revealed profound lymphopenia, decreased immunoglobulins and low uric acid levels (Table I). She also had a homozygous nonsense mutation (c.736C>T, p.Q246X) in exon 8 of the *ADA* gene. Antimicrobial prophylaxis, IVIG replacement and ERT were started as initial treatment. A matched related donor could not found and the family declined haplo-HSCT. At 3 months of age, the patient died due to severe pneumonia (5).

Table I. Clinical and laboratory findings of patients

Diagnosis	Case 1 (ADA-SCID)	Case 2 (ADA-SCID)	Case 3 (ADA-SCID)	Case 4 (ADA-SCID)	Case 5 (PNP-SCID)
Diagnosis of PID Age	2 months	2 months	1 month	2 months	12 months
Clinic presentation	Pneumonia	Family history Pneumonia	Family history Pneumonia	Vomiting, weight loss Oral thrush	Recurrent pneumonia Spastic paraparesis
ALC (mm^3)	350	310	360	130	240
CD3 (mm^3)	100	110	130	40	108
CD4 (mm^3)	60	64	80	10	48
CD8 (mm^3)	38	48	48	32	60
CD19 (mm^3)	150	150	120	50	70
NK (mm^3)	100	50	116	36	62
PHA response*	9.1/65.1	13.8/82.3	12.1/72.4	8.3/68.3	16.7/74.1
Uric acid (range , 2-6 mg/dL)	1.3	1.6	1.2	1.4	1.2
IgG (mg/dL)	210	190	170	140	270
IgA (mg/dL)	6.1	6.1	6.2	6.4	17
IgM (mg/dL)	16	12.2	12	14.2	48
Enzyme activity (nm/h/mg)	ADA: 0 (NR: 26.4±10)	ADA: 0 (NR: 26.4±10)	ADA: 0 (NR: 26.4±10)	ADA: 0 (NR: 26.4±10)	PNP: 17.2 (NR: 1354±561)
dAXP (%)	68.5(NR <1)	69.3 (NR <1)	70.4 (NR <1)	58.6 (NR <1)	0 (NR <1)
Genetic	c.736C>T p.Q246X	c.736C>T p.Q246X	c.736C>T p.Q246X	del[GAAGA] c.955-959	c.700 C>T p.R234X

ADA: Adenosine deaminase, **ALC:** Absolute lymphocyte count, **NR:** Normal range; dAXP, total deoxyadenosine nucleotides as a percent of total adenine nucleotides. **PHA:** Phytohemagglutinin, **PNP:** Purine nucleoside phosphorylase, *Stimulation index (patient/control).

Table II. Outcomes of patients

Cases no	PID	The age of PID diagnosis (months)	Treatment	Age of HSCT (months)	Outcome	Cause of death
Case 1	ADA-SCID	2	HSCT	4 (Haplo)	Exitus (+110 days)	Sepsis, GVHD
Case 2	ADA-SCID	2	HSCT	4 (MS)	Alive (at 9 months)	Alive
Case 3	ADA-SCID	1	ERT	ND	Exitus (at 3 months)	Pneumonia
Case 4	ADA-SCID	2	ERT	ND	Alive (at 9 months)	Alive
Case 5	PNP-SCID	12	HSCT	24 (UCB)	Alive (at 2.5 years)	Alive

ADA: Adenosine deaminase, **ERT:** Enzyme replacement treatment, **GVHD:** Graft-versus-host disease, **HSCT:** Hematopoietic stem cell transplantation, **MS:** Matched sibling, **ND:** Not done, **PID:** Primary immune deficiency, **PNP:** Purine nucleoside phosphorylase, **SCID:** Severe combined immune deficiency, **UCB:** Unrelated cordon blood

Case 4

A 2-month-old boy was admitted with vomiting and weight lost. There was second-degree consanguinity between the mother and father. Physical examination and laboratory findings revealed failure to thrive, oral thrush, profound lymphopenia, markedly decreased immunoglobulins, and low uric acid levels. The analysis of lymphocytes subsets indicated T-B-NK- SCID and genetic testing revealed a homozygous mutation (del[GAAGA] c.955-959) in exon 10 of the *ADA* gene (Table I). ERT, antimicrobial prophylaxis, and monthly IVIG replacement were started as initial treatment. A matched related donor could not be found and the family declined haplo-HSCT. Unrelated donor screening is continuing. He is now aged 9 months and well.

Case Associated with PNP

Case 5

A 12-month-old boy was admitted with pneumonia, recurrent oral thrush, and failure to thrive. There was third-degree consanguinity between the mother and father. He also had a history of a brother who died due to suspected primary immune deficiency (genetic etiology unknown) and he had experienced recurrent pneumonia in his first year of life. His immunologic evaluations revealed profound lymphopenia, markedly decreased immunoglobulins and low levels of uric acid. His laboratory findings indicated T-B-NK-SCID (Table I). Genetic testing revealed a homozygous mutation (c.700 C>T, p.R234X) in exon 6 of the *PNP* gene. Antimicrobial prophylaxis and monthly IVIG replacement were started. At 2 years of age, he was admitted with a six-month history of progressive spastic paraparesis. He was walking on fingertips and his condition was consistent with spastic paraparesis. A matched related donor could not found and unrelated donor screening was started. As the patient's family lived in Belgium, we contacted a tertiary center in Belgium for the transplantation. Unrelated cord blood (UCB) donor was found in Belgium. HSCT was performed at 26 months of age. He is now alive and well.

DISCUSSION

ADA deficiency occurs in about 10-20% of all cases of SCID, whereas PNP deficiency is diagnosed in less than 5% (5). Both ADA and PNP deficiency are genetically, metabolically, and clinically heterogeneous. Classic ADA deficiency is characterized by recurrent infections in the first months of life owing to complete or near complete absence of T, B, and NK-cells (T-B-NK-SCID). The B-cell defect in PNP deficiency is somewhat more variable. These patients may be diagnosed prior to clinical onset by neonatal screening for TRECs, or by tandem mass spectrometric screening for elevated levels of ADA or PNP substrates (where such screening is available). In some ADA deficient patients, who have a low level of residual enzyme activity (although less than 2% of normal), lymphocyte depletion is less severe at birth, but progresses over time. Such patients may be missed by TREC screening, and have been diagnosed with combined immune deficiency later in childhood and even as adults (3,6-8). In addition to SCID, ADA deficient patients may variably have non-immunologic defects, such as skeletal dysplasias, neurologic deficits, sensorineuronal deafness, hepatic dysfunction, and defects in cognitive and behavioral function (9). PNP deficiency is frequently associated with neurologic abnormalities, usually motor dysfunction, and autoimmune phenomena (1,5).

Herein, we report 5 patients with SCID (4 with ADA deficiency and 1 with PNP deficiency). All 5 patients were homozygous for null alleles, and therefore had the most severe disruption of metabolism. Three of the 4 ADA deficient patients presented with infections and failure to thrive early in life as in classic SCID patients. The fourth (case 3) was evaluated in her first month of life (not yet clinically ill) due to the family history of immune deficiency. None of the ADA deficient patients had non-immunologic abnormalities at diagnosis. The patient with PNP deficiency presented with infections and failure to thrive and was diagnosed at a year of age. He also presented with spastic paraparesis in his follow-up, which may lead to diagnosis of PNP deficiency in some cases before the onset of serious infections. ADA deficient patients have some treatment options including HSCT, ERT, and gene therapy (10,11). In the SCID patients, the major effective factor on the outcomes of HSCT is donor source. Overall survival rates were reported as 86% and 83% in MSD and matched family donor (MFD) HSCTs, respectively (9). In that study (9), survival rates were reported as 67%, 29%, and 43% in matched unrelated donor (MUD), mismatched unrelated donor (MMUD), and haplo-HSCT, respectively. ERT is another treatment option in ADA deficient patients. Developing anti-ADA antibodies is a major side effect associated with the use of ERT. In about 10% of treated patients, inhibitory antibodies lead to the enhanced clearance of ERT with subsequent decline in metabolic parameters and immune function (9). Since 2000, less than 40 patients have been treated with gene therapy as a treatment option in patients with ADA deficiency in Italy, the UK, and the USA, achieving substantial clinical benefit in the majority of them (1,10). Of these patients, all are alive andPEG-ADA is no longer required in 26 patients (10).

All of our 4 ADA deficient patients initially received ERT, and HSCT was subsequently performed in two of them. The patient (case 1, received haplo-HSCT) died at 8 months of age due to infection and GVHD. On the other hand, HSCT was successful in case 2 (received matched-HSCT from a MSD). In case 3, ERT was initially started but she died at 3 months of age due to severe pneumonia. Also, ERT was initiated in the last ADA deficient patient (case 4). Now he is alive and well with ERT at 9 months of age.

PNP deficiency is usually characterized by opportunistic infections in the first decade of life such as *Aspergillus fumigatus* and *Mycobacterium* infections. There is a progressively decreasing number of T-cells with often spared B-cells and NK-cells (T-B+NK+SCID). However, as in our PNP deficient patient, few PNP deficient patients present with severe infections in their first year of life with complete lack of B-cells (1,12,13). In this study, a PNP deficient patient was admitted with recurrent pneumonia and gait disturbance in his last 6 months of life (between ages of 1.5-2 years). In our PNP deficient patient, immunologic evaluation revealed profound lymphopenia with lack of T, B, and NK-cells as in classic T-B-NK-SCID patients.

In the differential diagnosis, a number of PIDs such as ataxia-telangiectasia, Nijmegen-Breakage syndrome, DNA ligase IV deficiency, Chediak–Higashi syndrome, severe congenital neutropenia, leukocyte adhesion deficiency type 2 and Hermansky–Pudlak syndrome type 2 are associated with neurologic symptoms and signs as well as PNP deficieny (14). Approximately more than half of the PNP deficient patients present with neurologic dysfunctions such as mental-motor retardation, spasticity, hypertonia, ataxia, and behavioral disturbances (15,16). As neurologic dysfunction, our PNP deficient patient only had progressive spastic paraparesis. In the treatment options, HSCT is the only curative treatment in patients with PNP deficiency (17). Also, recent case reports have demonstrated that HSCT might be beneficial and prevent further neurological deterioration when performed early in these patients (1). In our PNP deficient patient, UCB-HSCT was performed at 2 years of age and he is alive and well.

PNP is required as a substrate for the production of uric acid and lower serum uric acid levels are a known biochemical hallmark in patients with PNP deficiency. In contrast to PNP, the ADA enzyme is not associated directly with uric acid production (1,18). All the patients in this study had low uric acid levels. Low uric acid levels in patients with severe ADA deficiency may reflect failure to thrive, or possibly an effect on the renal excretion of uric acid, as abnormalities of kidney histology have been found at the autopsy of some infants with ADA deficiency (18).

The differential diagnosis of hypouricemia is made based on the fractional excretion of uric acid. Although hypouricemia with a reduced fractional excretion of uric acid is associated with xanthinuria, treatment with allopurinol, neoplasms and hepatic function abnormalities, hypouricemia with a high fractional excretion of uric acid is mainly caused by renal tubular dysfunctions such as Fanconi syndrome, use of salicylates and total parenteral nutrition (19). In the presented study, 4 patients (3 ADA and 1 PNP) presented with severe infections in the first months of life as in classic SCID patients. Also, the last ADA deficient patient had a positive family history for SCID. With the clinical presentations of the patients and genetic testing, other hypouricemia reasons were excluded in this study.

In conclusion, this study showed once again that physicians should be alerted for SCID by severe infections, positive family history as well as profound lymphopenia. Hypouricemia as an interesting finding should also alert doctors for ADA deficiency similar to patients with PNP deficiency.

Conflict of Interest

The authors declare that they have no conflict of interest

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