Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Case Report / Olgu Sunumu

Recurrent infections, neurologic signs, low serum uric acid levels, and lymphopenia in childhood: Purine nucleoside phosphorylase deficiency, an emergency for infants

Çocuklarda sık yineleyen enfeksiyonlar, nörolojik bulgular, serum ürik asit düşüklüğü ve lenfopeni: Pürin nükleozid fosforilaz eksikliği, çocukluk çağı acil hastalıklarından biri

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The known about this topic

Purine nucleoside phosphorylase (PNP) deficiency is a rare autosomal recessive disease that causes severe combined immunodeficiency. Patients present with frequently recurring infections, autoimmunity, growth and developmental retardation and neurologic findings in early childhood. The diagnosis is made by demonstrating deficiency of PNP activity or through PNP gene analysis. The association of T cell defects and a reduced level of serum uric acid is a warning. The only curative treatment is hematopoietic stem cell transplantation.

Contribution of the study

In this study, four patients with a diagnosis of PNP deficiency are presented with similar and different characteristics. In contrast to the literature, two of the patients were diagnosed before the age of one year and warning clinical and laboratory findings, which should be watched for early diagnosis, were emphasized. PNP deficiency is an immunologic emergency and should be diagnosed urgently. The number of studies related to genetic counselling and prenatal diagnosis should be increased.

Abstract

Purine nucleoside phosphorylase deficiency is one of the severe combined immunodeficiencies, which often clinically manifests with recurrent infections, neurologic symptoms and autoimmune diseases, and leads to thymocyte development and peripheral T cell activation defects. It is an immunologic emergency for childhood. In this case series, four cases with purine nucleoside phosphorylase deficiency were evaluated. Recurrent febrile infections and neuromotor developmental retardation were among the presenting symptoms in all cases. Absolute lymphocyte counts and serum uric acid levels were very low, and serum immunoglobulin levels were normal or slightly lower in all cases. The genetic molecular analysis of four patients revealed three predefined mutations in the purine nucleoside phosphorylase gene. Three of the four patients were lost due to sepsis during follow-up, and one patient

Öz

Pürin nükleozid fosforilaz eksikliği genellikle klinik olarak tekrarlayan enfeksiyonlar, nörolojik semptomlar ve otoimmün hastalıklarla bulgu veren, timosit gelişimi ve periferal T hücre aktivasyon kusuruna yol açan, ağır kombine immün yetmezliklerden biridir ve çocukluk çağı için bir immünolojik acildir. Bu olgu serisinde Pürin nükleozid fosforilaz eksikliği olan dört olgu değerlendirildi. Olguların hepsinin başvuru yakınmaları arasında tekrarlayan ateşli enfeksiyonlar ve nöromotor gelişim geriliği vardı ve laboratuvar bulguları incelendiğinde; hepsinde mutlak lenfosit sayısı ve serum ürik asit düzeyi çok düşük seviyelerde, serum immunglobulin düzeyleri ise normal ya da hafif düşüktü. Dört hastanın yapılan genetik moleküler incelemesinde Pürin nükleozid fosforilaz geninde üç tane daha önceden tanımlı mutasyon saptandı. Dört hastanın üç tanesi izlemde septik tabloda, bir tanesi de hematopoetik kök hücre

Cite this article as: Kütükçüler N, Bölük E, Tökmeci N, et al. Recurrent infections, neurologic signs, low serum uric acid levels, and lymphopenia in childhood: Purine nucleoside phosphorylase deficiency, an emergency for infants. Turk Pediatri Ars 2020; 55(3): 320–7.

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Received/Geliş Tarihi: 10.18.2018 **Accepted/Kabul Tarihi:** 21.06.2019

DOI: 10.14744/TurkPediatriArs.2019.83788

was lost due to veno-occlusive disease in the post-hematopoietic stem cell transplantation period. We presented these cases to emphasize that purine nucleoside phosphorylase deficiency should always be considered in patients with frequent recurrent infections, neurologic findings, low serum uric acid levels, and lymphopenia.

Keywords: Combined immunodeficiency, low serum uric acid levels, purine nucleoside phosphorylase deficiency

nakli sonrası dönemde veno-oklusiv hastalık nedeniyle kaybedildi. Çocuklarda sık yineleyen enfeksiyonlar, nörolojik bulgular, serum ürik asit düşüklüğü ve lenfopeni saptandığında Pürin nükleozid fosforilaz eksikliği tanısının mutlaka düşünülmesi gerektiğini vurgulamak amacıyla bu olgular sunulmuştur.

Anahtar sözcükler: Kombine immün yetmezlik, ürik asit düşüklüğü, pürin nükleozid fosforilaz eksikliği

Introduction

Purine nucleoside phosphorylase (PNP) deficiency (OMIM 164050) is an autosomal recessive disease that occurs as a result of the emergence of clinical findings with the toxic action of the purine metabolites deposited because of defective purine metabolism. In particular, the accumulation of deoxyguanosine triphosphate (dGTP) in erythrocytes leads to the increased formation of deoxyadenosine triphosphate (dATP) and inhibition of ribonucleotide reductase (1). Accumulating inosine, deoxyinosine, guanosine and deoxyguanosine cause a toxic action on T lymphocytes (1). As a result, the development of abnormal thymocytes and defective peripheral T cell activation causes an increased tendency to infections and immune dysregulation (2). In addition, impaired purine homeostasis leads to injury in some cell types and tissues (1, 2).

Adenosine deaminase (ADA) is a very important enzyme for purine metabolism and the emerging severe combined immune deficiency involves both T cells and B cells (3). In contrast to adenosine deaminase deficiency, PNP deficiency is characterized by a milder T cell defect (3). Patients with PNP deficiency generally present with growth and developmental retardation, recurrent severe infections, neurologic disorders, and autoimmunity (1, 2).

Combined immune deficiency caused by PNP deficiency is one of the most important emergency diseases of childhood. Purine nucleoside phosphorylase deficiency constitutes 4% of all cases of combined immune deficiencies (1, 2). The first case was published in 1970. According to the literature data, 67 cases of PNP were found in 49 families throughout the world in 2011 and this number reached 80 in 2014 (3).

In the literature, PNP deficiency has been generally included as single case presentations. By contrast, we have four patients whose diagnoses were confirmed through molecular examinations. In this study, we attempted to increase the awareness for this disease and determine the necessary strategies for early diagnosis and successful treatment by examining the clinical, laboratory, and genetic data of these patients, all of whom we lost.

Case 1

An eleven-month-old male patient had a history of recurrent pneumonia, bronchiolitis, and moniliasis from the neonatal period, and presented to our clinic with respiratory distress. There was consanguinity between the parents (third cousins). A physical examination revealed fever, mental and motor retardation, microcephaly, micrognathia, blue sclerae, and rales and rhonchi on lung auscultation. The laboratory test results were as follows: white blood cells (WBC): 7320/mm^3, absolute neutrophil count (ANC): 6310/mm^3, absolute lymphocyte count (ALC): 1010/mm^3, Hb: 10.6 g/dL, platelets (PLT): 353000 / mm^3, uric acid (UA): <2 mg/dL, immunoglobulin (Ig)-G: 1020 mg/dL, IgM: 54 mg/dL, IgA: 65 mg/dL, lymphocyte panel (LP): CD3 1.7%, CD19 12.5%, CD3-CD16/56 63%. A respiratory virus panel (SVP) revealed positive respiratory syncytial virus, and the blood Aspergillus antigen test was found to be positive. The purified protein derivative (PPD) test was found to be anergic. The interferon-gamma test and sweat test were negative. A diffuse myelinization defect was found on cranial magnetic resonance imaging (MRI). Despite treatment with multiple antibiotics and antifungals, resistant fever continued and the patient was lost in a picture of septic shock (Table 1). PNP IVS -3-18 G>A homozygous mutation was found in this patient (Table 2).

Case 2

A seven-month-old male patient presented to our clinic with symptoms of recurrent pneumonia and bronchiolitis as from birth. The family history revealed consanguinity between the parents (third cousins), and his brother (case 1) died with a diagnosis of PNP deficiency. A physical examination revealed retardation in neuromotor development, microcephaly, and rales and rhonchi on lung auscultation. The patient had resistant fever and respiratory distress. The laboratory test results were as follows: WBC: 3000/mm^3, ALC: 290/mm^3, ANC: 2790/mm^3, Hb: 11.5 g/dL, PLT: 201000/mm^3, UA: not measurable, IgG: 655 mg/dL, IgM: 43 mg/dL, IgA: 15 mg/dL, LP: CD3 31.5%, CD19 13%, CD4 8.8%, CD8 19.8%, CD3-CD16/56 43.8%, CD3 HLA DR 28.3%, T/B cell proliferation test: insufficient T cell proliferation response. Postero-anterior lung radiography revealed thymic hypoplasia. High-resolution computed tomography (HRCT) of the lung revealed subsegmental atelectasis and diffuse bronchiectasis in

Table 1. Demographic and clinical characteristics of the patients

Case	Age at the time of presentation	Sex (M/F)	Compliant at the time of presentation	Age at the time of diagnosis	Follow-up time	Consanguineous marriage	Clinical follow-up	Outcome	Reason of death
1	11 months	M	Cough, respiratory distress	12 months	1 month	Yes	Recurring bronchopneumonia, resistant fever	Exitus before HSCT	Sepsis
2	7 months	M	Cough, respiratory distress	8 months	6 months	Yes	Recurring bronchopneumonia, resistant fever	Exitus after HSCT	Veno-occlusive disease
3	46 months	M	Speech and walking impairment	48 months	3 months	Yes	Mental motor retardation, convulsions, autoimmune hemolytic anemia	Exitus before HSCT	Sepsis
4	13 months	F	Recurring neumonia	14 months	2 months	Yes	Mental motor retardation, Pneumonia, ARDS	Exitus before HSCT	Respiratory failure

M: Male; F: Female; HSCT: Hematopoietic stem cell transplantation; ARDS: Acute respiratory distress syndrome

Figure 1. Cerebral and cerebellar atrophy, deepening of the cerebral sulci on cranial computed tomography in case 3

the upper, middle, and lower lobes in the right lung and the upper and lower lobes in the left lung. Hematopoietic stem cell transplantation (HSCT) from 5/6 suitable unrelated donor cord blood was performed at the age of 13 months. Following hematopoietic stem cell transplantation, veno-occlusive disease and multiorgan failure developed while being followed up in our clinic, and the patient was lost in the second month after HSCT (Table 1). Homozygous PNP IVS -3-18 G>A mutation was found in the patient, and the parents were found to have the same mutation heterozygously (Table 2).

Case 3

A 46-month-old male patient had a history of recurrent bronchiolitis, inability to walk, inability to speak and seizure, and he presented to our clinic with respiratory distress. A physical examination revealed retardation in neuromotor development, fever, and rales and rhonchi on lung auscultation. There was consanguinity between the patents (second cousins). The laboratory test results were as follows: WBC: 3320 /mm^3, ANC: 2870/mm^3, ALC: 130/mm^3, Hb: 11.4 g/dL, PLT: 284000/mm^3, UA: 0.6 mg/dL, IgG: 741 mg/dL, IgA: 28 mg/dL, IgM: 38 mg/dL, LP: CD3 4.2%, CD19 0.46%, CD4 2.2%, CD8 2.7%, CD3-CD16/56 90%, CD3 HLA DR 2.4%. CMV viral load (DNA quantitative) was found as 3311 IU/mL. Respiratory virus panel revealed influenza, and stool examination demonstrated the presence of rotavirus. During hospitalization in the intensive care unit, tracheal aspirate culture and skin lesion tissue fungal examination revealed Candida albicans. Bronchiolitis obliterans was found on HRCT. During the follow-up, anemia developed and a direct Coombs test was found as (+++), suggesting a diagnosis of autoimmune hemolytic anemia.

Table 2. Lymphocyte count, serum immunoglobulin levels, lymphocyte subgroups and mutations found in our patients with purine nucleoside phosphorylase deficiency (11, 12)

	WBC /mm³	Absolute lymphocyte /mm³	IgG mg/dL	IgM mg/dL	IgA mg/dL	Uric acid mg/dL	CD 3%	CD 19%	CD3-CD16 /56 %	Mutation	Combined immuno -deficiency	Final status
Normal values	5000–12000	>1500	574–974*	58–138*	26–62*	2.0–5.5	60–70**	15–20**	5–15**			
1	7320	1010	1020	54	65	<2	1.7	12.5	63	Homozygous c.286-18G>A	T(-)B(-)NK(+)	Exitus
2	3080	290	655	43	15	<2	26	24	40	Homozygous c.286-18G>A	T(-)B(+)NK(+)	Exitus
3	3320	130	741	38	28.6	0.6	4.2	0.4	90	Homozygous c.172C>T (p.Arg58Ter)	T(-)B(-)NK(+)	Exitus
4	2800	300	548	17.3	6.1	1.7	76	1.8	23	Homozygous c.700C>T (p.Arg234)	T(+)B(-)NK(+)	Exitus

WBC: White blood count; IgA: Immunoglobulin-A; IgG: Immunoglobulin-G; IgM: Immunoglobulin-M

Figure 2. Appearance of bilateral paramediastinal infection on computed tomography of the thorax suggesting invasive fungal infection in the lung in case 4

In the follow-up, resistant convulsions occurred. Cranial computed tomography showed cerebral, cereballar atrophy and deepening of cerebral sulci (Fig. 1). Fully suitable HSCT from the father was planned, but the patient was lost before HSCT could be performed with a picture of resistant fever, septic shock, and multiorgan failure under multiple antibiotherapy, antifungal and antiviral treatment (Table 1). A homozygous p.R58X stop codon mutation was found in the patient, and the parents were found to have heterozygous c.172 C>T (p.Arg58Ter) mutations (Table 2).

Case 4

A 12-month-old female patient who had a history of recurrent pneumonia and broncholitis presented to our clinic with respiratory distress. There was consanguinity between the parents (third cousins). A physical examination revealed retardation in neuromotor development and rales and rhonchi on lung auscultation. The laboratory test results were as follows: WBC: 2800/mm^3, ALC: 300/mm^3, ANC: 2500/mm^3, Hb: 9.5 g/dL, UA: 1.7 mg/dL, IgG: 548 mg/dL, IgM: 17.3 mg/dL, IgA: 6.1 mg/dL, LP: CD3 76%, CD19 1.8%, CD4 59%, CD8 17%, CD3-CD16/56 20.8%, CD3$^+$ HLA DR 75.3%, CMV viral load (DNA quantitative): 842 IU/mL. Coagulase-negative staphylococcus was grown in a blood culture. Coronavirus and Human Bocavirus were isolated on SVP. HRCT revealed bronchiectasis and nodular consolidation areas and ground-glass opacity in the lower lobe of the right lung and the upper lobe of the left lung. On cranial magnetic resonance imaging, cerebral sulci were reported to be deepened and enlarged. Fungal pneumonia and acute

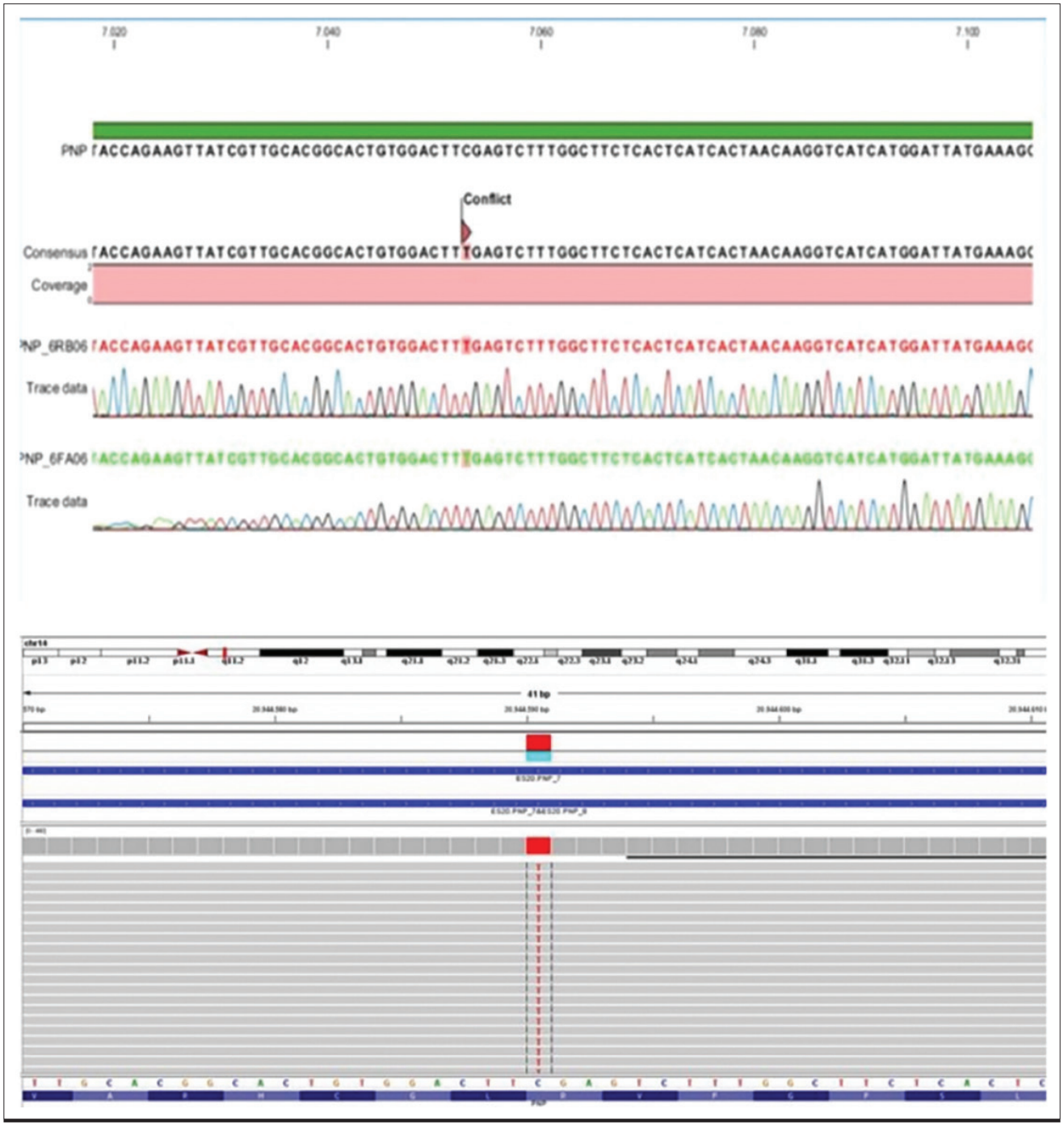

Figure 3. Homozygous nonsense mutation in exon 6 (c.700 C>T) (P.Arg234Ter) in the purine nucleoside phosphorylase gene in case 4

respiratory distress syndrome (ARDS) developed during follow-up (Fig. 2). Despite multiple antibiotherapy, antifungal and antiviral treatment, resistant fever and respiratory distress continued, and the patient, who was being followed up with a diagnosis of fungal pneumonia and ARDS, was lost with severe respiratory failure (Table 1). A homozygous p.Arg234Ter stop codon mutation was found in the patient (Fig. 3, Table 2).

Written consent was obtained from the patients' parents. Plasma PNP activity was not studied in any of the patients.

Discussion

It is understood that almost all patients with PNP deficiency published in the literature were diagnosed after the age of two years (3, 4). Two of our patients were diagnosed before the age of one year, one patient presented

at the age of 13 months, and another patient presented at the age of 46 months with a clinical picture of severe combined immune deficiency; considering the lymphopenia, reduced uric acid levels, and neurologic findings in particular, a genetic evaluation was performed and a definite diagnosis of PNP deficiency was made.

Progressive neurologic disorders and dystonic movements are observed in more than half of all patients with PNP deficiency. Developmental retardation, hypertonia, spasticity, tremors, ataxia, and motor retardation are observed frequently. Cranial MRI reveals cerebral cortical and cerebellar atrophy and white matter demyelination (1). Somech et al. (3) reported marked hypotonia and mental motor retardation at the time of presentation in three patients whose symptoms included fever and respiratory distress. Ozkınay et al. (5) found spastic paraparesis in the lower extremity on physical examination at presentation in a 2-year-old female patient who attended hospital because of recurring fever. All our patients had retardation in neuromotor development, and one patient had recurring afebrile convulsions. Cranial MRI was performed in all patients; severe myelinization defects were found in two patients, bilateral mastoiditis was found in one patient, and no other cerebral or cerebellar MR finding was detected. The cranial MRI of the final patient revealed no findings except for deepening and enlargement in the cerebral sulci. The pathogenesis of neurologic dysfunction in patients with PNP deficiency has not yet been elucidated (3).

Patients are generally lost with septicemia. Infections with Candida albicans, Pneumocystis jiroveci and herpes simplex virus, which are opportunistic pathogens, have a severe and fatal course. Aytekin et al. (6) presented two female patients with PNP deficiency who had a fatal course, reporting that one of these patients had liver abscess caused by Aspergillus fumigatus, and the other had lymphadenitis caused by mycobacterium tuberculosis complex, and both had sclerosing cholangitis. Tuberculosis was not found in our patients. As emphasized in the literature, two of our four patients were lost in a clinical picture of septicemia in the preparation phase before HSCT. One patient died of respiratory failure during severe pulmonary infection and one patient died of veno-occlusive disease following HSCT. As emphasized by Aytekin et al., (6) PNP deficiency is a fatal disease. This team lost their two patients, and our four patients died despite all efforts when they were aged between 12 and 18 months after a considerably short follow-up period. Therefore, PNP deficiency is an actual emergency disease of childhood that leads to severe combined immune deficiency.

In terms of the immunologic variety of patients, Somech et al. (3) found the value of IgA to be normal and values of IgG and IgM to be low in their patients who were diagnosed as having PNP deficiency following investigations because of recurrent febrile infections. Aytekin et al. (6) found IgG, IgA, and IgM to be normal in a 7-year-old patient among two siblings diagnosed as having PNP deficiency, and they found normal levels of IgG and low levels of IgA and IgM in the 3-year-old sister. The flow cytometry result of these two sisters was as follows: T(-)B(-)NK(-). Ozkınay et al. (5) found the values of IgG, IgA, and IgM to be within the normal limits in a 6-month-old patient who was diagnosed as having PNP deficiency. Celmeli et al. (7) found values of IgG, IgA, and IgM to be within the normal limits in a 13-year-old female patient who was investigated because of recurring sinopulmonary infections. The flow cytometry result of this patient was as follows: T(-)B(+)NK(+). Aytekin et al. (8) found IgA values to be normal and IgG and IgM values to be low in their 13-month-old male patient with PNP deficiency. The flow cytometry result of this patient was as follows: T(-)B(-)NK(-). In our case series, the IgM value was found to be low and the IgG and IgA values were normal in Case 1 and 3. In Case 2, the IgA and IgM values were low and the IgG value was normal. In Case 4, the IgG, IgA, and IgM values were all found below the normal limit. The flow cytometry result was found to be T(-)B(+)NK(+) in Case 1 and 2, T(-)B(-)NK(+) in Case 3, and T(+)B(-)NK(+) in Case 4.

Forty different mutations were identified until 2011 in the patients with PNP deficiency (3). Sixty-three percent of these point mutations are transition mutations (3). Cooper and Krawczak (4) reported that 32% of all point mutations occurred in the CpG sequence. The first Turkish patient with PNP deficiency was published by Özkınay et al. (5) in 2007. The Ala117Thr mutation that was found in this patient was not found in our patients. An Ala117Thr mutation was also shown by Aytekin et al. (6) in two sisters in 2010. The three different mutations identified in our patients have been identified before, but to the best of our knowledge, they were demonstrated in Turkish patients for the first time.

The only curative treatment for PNP deficiency is HSCT. In this way, purine nucleoside metabolism improves in the non-neuronal cell population, and neuronal dysfunction is stabilized (3). Celmeli et al. (7) reported successful HSCT from an HLA-identical non-relative donor following a low-intensity conduction regime in a 13-year-old patient with late-onset PNP deficiency. Aytekin et al. (8) reported that HSCT was performed in a 13-month-old baby with PNP deficiency without performing a conduc-

tion regime, immunologic reconstitution occurred at the end of three years in the post-transplant follow-up, the patient's speech and cognitive skills were good, but spasticity in the lower extremities persisted. Similarly, Baguette et al. (9) reported that developmental retardation was permanent in a patient with PNP deficiency despite successful HSCT. In contrast to these patients, Brodszki et al. (10) emphasized that their 2-year-old patient who underwent HSCT showed very successful improvements both immunologically and neurologically; the level of fine motor skills reached to 3–4 years of age when the patient was aged 55 months, and the speech, social and emotional skills also reached the same age levels. Only one of our patients had the chance of undergoing HSCT but was lost because of a complication of veno-occlusive disease.

We here report four subjects to emphasize the importance of early diagnosis in combined immune deficiency caused by PNP deficiency to once again remind that this diagnosis should be considered primarily in patients with frequent severe infections in association with low uric acid levels, lymphopenia, and neurologic findings. Also, to stress that very successful prenatal counselling can be performed in these cases if a molecular pathology is known.

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.E.K., N.K.; Design - N.E.K., G.A., N.K.; Supervision - N.E.K., A.A., N.K.; Data Collection and/or Processing - E.B., N.T., N.E.K.; Analysis and/or Interpretation - A.A., N.E.K., N.K.; Literature Review - E.B., N.T., N.E.K.; Writing - E.B., N.T.; Critical Review - N.E.K., A.A., N.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Katılımcılardan yazılı onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - N.E.K., N.K.; Tasarım - N.E.K., G.A., N.K.; Denetleme - N.E.K., A.A., N.K.; Veri Toplanması ve/veya İşlemesi - E.B., N.T., N.E.K.; Analiz ve/veya Yorum - A.A., N.E.K., N.K.; Literatür Taraması - E.B., N.T., N.E.K.; Yazıyı Yazan - E.B., N.T.; Eleştirel İnceleme - N.E.K., A.A., N.K.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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