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CASE REPORT

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Purine Nucleoside Phosphorylase Deficiency Presenting with Neurological Involvement: A Case Report of Two Siblings

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ABSTRACT

Purine nucleoside phosphorylase (PNP) deficiency is a rare immunodeficiency syndrome generally characterized by profound T cell deficiency and variable B cell function. More than half of PNP-deficient patients present with neurological dysfunction, with manifestations such as mental and motor retardation, spasticity, hypertonia, ataxia, and behavioral disturbances.

Here, we report two siblings diagnosed with PNP deficiency in early infancy. Our patients had developmental delays, and their immunological findings indicated T-B+NK+ leaky/atypical severe combined immune deficiency. The patients are being treated with regular intravenous immunoglobulin replacement, as well as trimethoprim-sulfomethoxazole and fluconazole, for prophylaxis in preparation for transplantation.

These cases draw attention to the possibility of primary immune deficiency in patients with recurrent infections and lymphopenia. In addition, PNP deficiency should be kept in mind in the presence of developmental delay, low uric acid levels, and lymphopenia.

Keywords: Combined immune deficiency, development delay, purine nucleoside phosphorylase deficiency, lymphopenia

INTRODUCTION

Purine nucleoside phosphorylase (PNP) is a ubiquitously expressed enzyme of the purine salvage pathway. When there is a deficiency or a lack of activity of PNP, the purine salvage pathway is impaired. This build-up is especially harmful to T cells, as they are highly susceptible to imbalances in nucleotide metabolism (1).

PNP deficiency, a lethal autosomal recessive metabolic disorder, manifests with immunodeficiency, autoimmune hemolytic anemia, and diverse neurological symptoms such as ataxia and developmental delay (2). Accounting for approximately 4% of profound T cell deficiencies, PNP deficiency necessitates hematopoietic stem cell transplantation (HSCT) for definitive treatment (3). In this report, two siblings with PNP deficiency were diagnosed through exome sequencing, primarily due to neurological symptoms.

CASE 1

A three-year-old male, previously developing normally until 8 months, was diagnosed with PNP deficiency. Parents observed developmental delay and ataxia by 12 months, prompting consultation with a pediatric neurologist. According to his medical records recurrent upper respiratory tract infections started after 12 months of age. He is the first child of consanguineous parents. His mother and father are healthy. On physical examination; he had clonus, increased deep tendon reflexes, and spastic diplegia but no dysmorphic features.

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The patient exhibited lymphopenia (absolute lymphocyte count: 730 cells/mm^3), a recurrent finding in previous examinations. Other hematological parameters and serum immunoglobulin levels were normal. He displayed moderately reduced CD4$^+$ and CD8$^+$ T cell numbers, while B cell and natural killer cell counts were normal. CD45RA$^+$ naive T cells constituted 2.5% of CD4$^+$ T cells. Maternal engraftment was absent, recent thymic emigrants were not detected, and T regulatory cells were reduced. There was ¼ of control CD25 activation of T cells with phytohemagglutinin (PHA) (Table I).

Serum uric acid level was at the lower limit of the normal. Adenosine deaminase enzyme activity was normal, and erythrocyte PNP activity extracted from dried blood spots measured 43.6 nmol/h/mg (normal level: 1,354±561 nmol/h/mg). Exome sequencing analysis showed a homozygous missense mutation in the *PNP* gene, resulting in a c.349G>A amino acid substitution which changes alanine 117 to threonine in exon 4 (A117T). This variant has been previously documented in siblings with features of PNP deficiency OR as pathogenic(OMIM #613179).

CASE 2

A 10-month-old female patient was evaluated, considering her older brother's diagnosis of PNP deficiency. The patient exhibited significant motor developmental delay, characterized by an inability to sit without support and stand. Furthermore, the patient had intermittent fever episodes but no prior hospitalizations.

Table I. Immunological data of these cases.

	Case 1 (3y 10 months)	Normal Range	Case 2 (10 months)	Normal Range
White Blood Cell (mm^3)	4230	4000-10400	12600	5600-13110
ALC (mm^3)	730	1500-5200	590	3200-10800
IgA (mg/dl)	163	56.2-81.7	25.9	21.06-37.7
IgM (mg/dl)	360	107-136	121	67-94
IgG (mg/dl)	945	778.5-901.1	511	499-638
IgE (IU/L)	225	0-230	<19.4	0-230
CD3$^+$T %	48	53.6-80.7	34.8	57.6-81.2
CD3$^+$T (Absolute Values / µl)	413	1200-4706	205	1945-7129
CD3$^+$CD4$^+$T%	21	23.6-52.5	18.2	30-55.8
CD3$^+$CD4$^+$T (Absolute Values / µl)	181	458-2755	107	1161-4819
CD3$^+$CD8$^+$T%	17.5	12.1-35.7	14.2	11-33
CD3$^+$CD8$^+$T (Absolute Values / µl)	151	310-2250	84	165-1878
CD16$^+$56$^+$NK %	9.7	3.5-22.2	17.9	2.5-17.9
CD16$^+$56$^+$NK (Absolute Values / µl)	83	88-1393	106	130-1073
CD19$^+$B%	9.1	8.4-28.5	17.6	9.1-35.9
CD19$^+$B (Absolute Values / µl)	78	205-1341	104	467-3112
CD4$^+$CD45RA (% of CD4)	2.5	54.9-83.1	15.6	62.9-87.8
CD4$^+$CD45RO (% of CD4)	93.6	12.8-42.5	79.7	9.6-30.8
Recent Timic Emigrant (RTE) (CD4$^+$CD45RA$^+$CD31$^+$)	0	47.9-77	7.7	47.9-77
T cell response to PHA	¼ of control		½ of control	
Regulatory T Cell (CD4$^+$CD25$^+$FOXP3$^+$)	0		%9.1	
Isohemagglutinins	1/32(Anti A)	>1/8	1/16 (Anti B)	>1/8
Anti HbS (mg/dl)	Negative		Positive	
Anti Tetanus antibodies (ıu/mL)	0.19	>0.1	0.23	>0.1
Serum uric acid (mg/dl)	2.7	2.4-5.7	2.6	2.4-5.7
PNP activity (nmol/h/mg)	43.6	1354 ± 561	11.7	1354 ± 561

On physical examination she could hold her head steady but could not sit without support. Immunological assessments indicated lymphopenia (590 mm^3), low T cell counts, normal B and NK cell counts, and a reduced $CD45RA^+$ naive-phenotype T cell percentage. (Table I) No maternal engraftment was detected. PNP activity was low (11.7 nmol/h/mg). The sister, like her brother, is homozygous for the same PNP pathogenic variant. Parents are heterozygous. Pneumocystis carinii prophylaxis and immunoglobulin replacement therapy were started. Both patients are being prepared for HSCT. Informed consent was obtained from the patient's parents for publication.

DISCUSSION

Two siblings with genetically diagnosed PNP deficiency are reported. The first case initially presented with neurological symptoms, while lymphopenia was detected earlier. The sister received an early diagnosis due to heightened suspicion. Another patient, a 13-year-old with the same variant, exhibited "late-onset PNP deficiency" with bronchiectasis, severe VZV, HSV keratitis, and neurological symptoms, successfully treated with HSCT (4). Tragically, two younger sisters with the same variant (7 and 3 years old) succumbed to systemic aspergillosis and disseminated mycobacterial infection before HSCT (5). Unlike other cases in the literature, the reported patients did not have a history of severe infections.

PNP deficiency, known for immune abnormalities, exhibits neurological manifestations in over 50% of cases, often presenting as motor deficits preceding immune defects (6). In the described patients, neurological findings were prominent before immunological abnormalities, suggesting a non-immune-related mechanism.

Combined immune deficiency is a syndrome caused by pathogenic variants in several genes that are crucial for the development and function of both T and B cells, and it may also affect NK cells. According to the 2022 IUIS phenotypical classification update, PNP deficiency is classified as a combined immune deficiency with associated or syndromic features (7). To the current criteria, our patients were compatible with leaky/atypical SCID that is rarely observed in PNP deficiency (8).

A comprehensive approach for PNP deficiency involves supportive treatments to minimize the risk of infection and enhance neurological development before corrective stem cell transplantation (9). HSCT effectively restores immunity, but its long-term neurological effects are unknown (9,10).

Both siblings exhibited similar neurological and immunological findings. Lymphopenia, initially overlooked in the first case, underscores the importance of considering PNP deficiency in patients with neurological delays, low uric acid levels, and lymphopenia. The diagnosis may be delayed if infectious findings appear later than neurological symptoms, making accompanying lymphopenia a crucial warning sign. Clinicians should be alert for immune deficiency in cases involving neuromotor developmental delay and lymphopenia.

Conflict of Interest
The authors declare no conflict of interest.

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Author Contributions
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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