Journal of Child Neurology

http://jcn.sagepub.com

Purine Nucleoside Phosphorylase Deficiency in a Patient With Spastic Paraplegia and Recurrent Infections

Ferda Ozkinay, Sacide Pehlivan, Huseyin Onay, Paul van den Berg, Fadil Vardar, Guldane Koturoglu, Guzide Aksu, Durisehvar Unal, Hasan Tekgul, Sema Can and Cihangir Ozkinay

J Child Neurol 2007; 22; 741
DOI: 10.1177/0883073807302617

The online version of this article can be found at:
http://jcn.sagepub.com/cgi/content/abstract/22/6/741

Published by:
SAGE
http://www.sagepublications.com

Brief Communication

Journal of Child Neurology
Volume 22 Number 6
June 2007 741-743
© 2007 Sage Publications
10.1177/0883073807302617
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

Purine Nucleoside Phosphorylase Deficiency in a Patient With Spastic Paraplegia and Recurrent Infections

Ferda Ozkinay, MD, Sacide Pehlivan, PhD, Huseyin Onay, MD, PhD, Paul van den Berg, PhD, Fadil Vardar, MD, Guldane Koturoglu, MD, Guzide Aksu, MD, Durisehvar Unal, PhD, Hasan Tekgul, MD, Sema Can, MD, and Cihangir Ozkinay, MD

Purine nucleoside phosphorylase deficiency is a rare autosomal recessive immunodeficiency disease. The characteristic features of the disease include severe T cell immune defects with recurrent infections, a failure to thrive, and progressive neurological findings. To date, 35 cases of purine nucleosidase phosphorylase deficiency have been reported worldwide. A 2-year-old female patient was hospitalized due to recurrent infections starting from 6 months and a fever that had continued for a month. The parents were first cousins. Physical examination showed a failure to thrive, herpetic lesions around the lips, painful lesions on the tongue and the buccal mucosa, lung infection, and spastic paraparesis in the lower extremities. She had motor and mental retardation. Laboratory tests revealed lymphopenia; low CD3, CD4, and CD8 counts; normal immunoglobulin levels; low uric acid; and very low purine nucleoside phosphorylase enzyme activity (1.4 nmol/h/mg; normal range, 490-1530). DNA sequencing of the purine nucleosidase phosphorylase gene revealed a missense homozygous mutation, a G to A transition at exon 4 position 64 (349G>A transition), which led to a substitution of alanine by threonine at codon 117 (Ala117Thr). Both parents were heterozygous for the mutation. This is the second purine nucleosidase phosphorylase deficient case to have been presented and carrying this mutation worldwide. Various antibiotics, antifungal drugs, and intravenous immunoglobulin were used to treat the infections during her 3 months. This form of treatment proved to be unresponsive, resulting in her subsequent death at 26 months of age.

Keywords: purine nucleoside phosphorylase deficiency

Purine nucleosidase phosphorylase deficiency causes severe immune deficiency and is a very rare autosomal recessive disease.[1-3] Approximately 35 cases of purine nucleoside phosphorylase deficiency have been reported worldwide. Patients with purine nucleosidase phosphorylase deficiency have a profound T cell immune defect and variable humoral abnormalities resulting in recurrent bacterial, viral, and fungal infections. Neurological manifestations such as severe spasticity, failure to thrive, mental retardation, and autoimmune diseases are other common features of the disease.[3,4]

From the Department of Pediatrics (FO, HO, FV, GK, GA, HT, SC), Department of Biology (SP), and Department of Medical Genetics (CO), Faculty of Medicine, Ege University, Izmir, Turkey; Department of Clinical Genetics, University Medical Center, Erasmus University, Rotterdam, Netherlands (PB); and Department of Molecular Genetics, Faculty of Science, Bogazici University, Istanbul, Turkey (DU).

Address correspondence to: Huseyin Onay, MD, Tıp Fakultesi, Cocuk Sagligi ve Hastaliklari AD, Genetik BD, Ege Universitesi, 35100, Izmir, Turkey; e-mail: honay@med.ege.edu.tr.

Ozkinay F, Pehlivan S, Onay H, et al. Purine nucleoside phosphorylase deficiency in a patient with spastic paraplegia and recurrent infections. *J Child Neurol*. 2007;22:741-743.

The purine nucleosidase phosphorylase gene is located at 14q13 and contains 1418 bp with a coding sequence of 870 bp.[5,6]

Molecular analysis of previous patients with purine nucleosidase phosphorylase deficiency has revealed 18 different mutations in the gene.[6-11] This report describes a homozygous missense mutation in a Turkish patient with purine nucleosidase phosphorylase deficiency born to consanguineous parents. This is the first known Turkish patient with purine nucleosidase phosphorylase deficiency to have carried this particular mutation and the second purine nucleosidase phosphorylase–deficient case to have carryied this mutation worldwide.

Materials and Methods

Immunological studies, including measurements of immunoglobulin and lymphocyte subgroup levels, were performed using standard clinical methodologies. Adenosine deaminase and purine nucleosidase phosphorylase enzyme activities in skin fibroblasts were kindly determined for us by Dr Paul van den Berg (as described in Kleijer et al[12]) at the

Clinical Genetics Laboratory, Erasmus University (Rotterdam, the Netherlands).

Genomic DNA was isolated from peripheral blood cells by standard techniques. To amplify exons 1 to 6 of the purine nucleosidase phosphorylase gene, polymerase chain reaction (PCR) was performed using the primers designed as previously described.[7] All PCR products were sequenced by the dye termination method using a DNA sequencing kit (PerkinElmer, Wellesley, Mass) and analyzed using the ABI Prism 310 sequence analyzer (Applied Biosystems, Foster City, Calif).

Case

A 26-month-old Turkish girl was referred to our hospital for recurrent infections, febris continuous, and failure to thrive. The parents were first cousins. She was the first child and born by normal spontaneous delivery with a birth weight of 2600 g. Her motor and mental developments were retarded. She gained head control at 7 months, sat at 1.5 years, and was unable to walk. She was only able to say a few words. She experienced recurrent upper and lower respiratory tract infections, and she had been hospitalized twice in other hospitals within the past 3 months. During her hospitalization, she was diagnosed as having bronchopneumonia, oral thrush, and spastic paraplegia for which she was given various antibiotics and antimycotics such as penicillin, vancomycine, ceftazidin, meropenem, and fluconazole. Complete blood counts showed leucopenia and severe lymphopenia. Immunoglobulin levels were normal. Despite extensive antibiotherapy, no remarkable improvement was obtained, and she remained febrile.

On admission, at 26 months, her weight was at the 3rd percentile (10.2 kg), height at the 25th percentile (84 cm), and head circumference at the 2nd percentile (45.5 cm). She had a high fever (39.5°C), oral thrush, herpetic lesions around the lips, membranous pharyngitis, and a lower respiratory tract infection. She also had marked spasticity with brisk reflexes in the lower extremities. She was unable to walk.

Laboratory tests revealed anemia (hemoglobin: 7.5 g/dL, hematocrit: 24%) and leucocytopenia (2090/μL) with lymphocytopenia (520/μL). Lymphocyte subgroup analysis showed low CD3 (5%), CD4 (3%), CD8 (3%), and CD25 (6%) and normal CD19 (25%) cells. Both T cell and B cell parameters were repeated after 1.5 months, but similar results were obtained. Bone marrow analysis showed erythrodysplasia, giant erythroblasts, normal ranges of myeloid cells, and very low counts of lymphoid cells. Immunoglobulin levels were normal. Serum uric acid levels were measured 3 times and were found to be markedly lower (0.6, 0.5, 1.4 mg/dL) than the normal levels (2-6 mg/dL). Her cranial magnetic resonance imaging showed mild cerebral atrophy and bilateral hypomyelinization in the globus pallidus and on preaquaductal areas. It was assumed that they may have resulted from a neurometabolic disorder.

Table 1. The Activity of Purine Nucleosidase Phosphorylase and Adenosine Deaminase in the Patient's Fibroblasts

Enzyme Activity in Fibroblasts	Patient	Normal
Adenosine deaminase	1060 nmol/h/mg	390-1150 nmol/h/mg
Purine nucleosidase phosphorylase	1.4 nmol/h/mg	490-1350 nmol/h/mg

Based on the severe T cell depletion, normal B cell level, low uric acid levels, and the neurological findings, a purine metabolism disorder associated with immune deficiency was considered as a final diagnosis for the patient. Purine nucleosidase phosphorylase and adenosine deaminase activities were measured in skin fibroblasts. Purine nucleosidase phosphorylase enzyme activity was deficient, whereas adenosine deaminase activity was normal (Table 1).

Clinically, the patient developed severe bronchopneumonia, which proved unresponsive to a varying number of antibiotics and antifungal treatments. She required intubation. Epstein-Barr virus viral capsid antigen immunoglobulin was found positive in her serum. Herpes simplex virus was identified from herpetic lesions around the lips, and acyclovir was given. She experienced tonic-clonic convulsions. Despite 2 months of intensive therapy, including blood transfusion, anticonvulsants, and intravenous immunoglobulin, no improvement was obtained. She remained febrile, and the disease followed a fatal course. She died at the age of 26 months.

Molecular Studies

Sequence analysis of amplified fragments of the purine nucleosidase phosphorylase gene revealed a missense homozygous mutation, a G to A transition at exon 4 position 64 (349G>A transition), which led to a substitution of alanine by threonine at codon 117 (Ala117Thr). Both parents were heterozygous for this mutation, confirming the autosomal recessive inheritance.

Discussion

Purine nucleosidase phosphorylase and adenosine deaminase are enzymes in the purine metabolic pathway, and their deficiencies cause immunodeficiency disorders. In adenosine deaminase deficiency, both cellular and humoral immunity are disturbed, whereas in purine nucleosidase phosphorylase deficiency, cellular immunity is selectively disturbed.[2,3] Establishing the diagnosis of purine nucleosidase phosphorylase deficiency is made difficult because of

its rarity and the variability of its clinical and immunological manifestations. It has been reported that in most cases of purine nucleosidase phosphorylase deficiency, patients die during childhood, but following the onset of the disease, the symptoms and the clinical course vary widely.[7,13,14]

In the patient presented, the symptoms of her severe immunological deficiency and neurological deterioration started somewhat earlier than in most previously reported cases. Tabarki et al[8] described 2 siblings carrying the same mutation. Those 2 siblings showed predominant central nervous system involvement and immunological symptoms that did not develop until the third year of age. With regard to the findings in Tabarki et al's cases and our case, it may be considered that the clinical findings of patients with purine nucleosidase phosphorylase deficiency having the Ala117Thr missense mutation are likely to vary in degree. There may be other genes that modify the clinical presentation.

Infections, malignancies, and neurological symptoms are the most important problems facing patients with purine nucleosidase phosphorylase deficiency. Antibiotherapy and other methods of intervention cannot change the fatal clinical course of the disease. Bone marrow transplantation has been successfully performed in other subgroups with severe common immune deficiencies.[15] But in patients with purine nucleosidase phosphorylase deficiency, it has been reported that neurodevelopmental manifestations progress despite immune reconstruction achieved by bone marrow transplant.[16] In the patient presented, it was impossible to perform a bone marrow transplant as a result of her severe clinical symptoms, which she experienced until death.

Different types of mutations have been described in the purine nucleosidase phosphorylase gene, the most common of which is a transition mutation with the frequency of 75%[10].

The mutation (G to A transition at exon 4 position 64) described in this case resulted in an amino acid substitution (alanine to threonine) in the protein and revealed very low levels of enzyme activity (Table 1). Extremely diminished enzyme activity might explain the severe clinical outcome in this case. However, there has been no study investigating the correlation between the enzyme activity and the clinical symptoms.

This is the first Turkish purine nucleosidase phosphorylase deficient case and the second case recorded worldwide having the mutation of Ala117Thr. There might be an ancestral link with the case by Tabarki et al.[8]

In conclusion, purine nucleosidase phosphorylase deficiency shows a wide variety of neurological and immunological symptoms. The patients who have the mutation Ala117Thr in the purine nucleosidase phosphorylase gene can show different phenotypes. Because of the very low numbers of patients with purine nucleosidase phosphorylase deficiency analyzed at a genetic level, further cases are needed to make phenotype-genotype correlations.

References

1. Giblett ER, Ammann AJ, Wara DW, et al. Nucleoside-phosphorylase deficiency in a child with severely defective T-cell immunity and normal B-cell immunity. *Lancet*. 1975;1:1010-1013.
2. Hershfield MS, Mitchell BS. *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York, NY: McGraw-Hill; 2001.
3. http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=164050
4. Markert ML. Purine nucleoside phosphorylase deficiency. *Immunodefic Rev*. 1991;3:45-81.
5. Snyder FF, Jenuth JP, Mably ER, Mangat RK. Point mutations at the purine nucleoside phosphorylase locus impair thymocyte differentiation in the mouse. *Proc Natl Acad Sci USA*. 1997; 94:2522-2527.
6. Williams SR, Gekeler V, McIvor RS, Martin DW Jr. A human purine nucleoside phosphorylase deficiency caused by a single base change. *J Biol Chem*. 1987;262:2332-2338.
7. Moallem HJ, Taningo G, Jiang CK, et al. Purine nucleoside phosphorylase deficiency: a new case report and identification of two novel mutations (Gly156A1a and Val217Ile), only one of which (Gly156A1a) is deleterious. *Clin Immunol*. 2002;105:75-80.
8. Tabarki B, Yacoub M, Tlili K, et al. Familial spastic paraplegia as the presenting manifestation in patients with purine nucleoside phosphorylase deficiency. *J Child Neurol*. 2003;18:140-141.
9. Aust MR, Andrews LG, Barrett MJ, et al. Molecular analysis of mutations in a patient with purine nucleoside phosphorylase deficiency. *Am J Hum Genet*. 1992;51:763-772.
10. Dalal I, Grunebaum E, Cohen A, Roifman CM. Two novel mutations in a purine nucleoside phosphorylase (PNP)-deficient patient. *Clin Genet*. 2001;59:430-437.
11. Markert ML, Finkel BD, McLaughlin TM, et al. Mutations in purine nucleoside phosphorylase deficiency. *Hum Mutat*. 1997; 9:118-121.
12. Kleijer WJ, Hussaarts-Odijk LM, Los FJ, et al. Prenatal diagnosis of purine nucleoside phosphorylase deficiency in the first and second trimesters of pregnancy. *Prenat Diagn*. 1989;9:401-407.
13. Rijksen G, Kuis W, Wadman SK, et al. A new case of purine nucleoside phosphorylase deficiency: enzymologic, clinical, and immunologic characteristics. *Pediatr Res*. 1987;21:137-141.
14. Watson AR, Evans DI, Marsden HB, et al. Purine nucleoside phosphorylase deficiency associated with a fatal lymphoproliferative disorder. *Arch Dis Child*. 1981;56:563-565.
15. Buckley RH. Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. *Annu Rev Immunol*. 2004;22:625-655.
16. Baguette C, Vermylen C, Brichard B, et al. Persistent developmental delay despite successful bone marrow transplantation for purine nucleoside phosphorylase deficiency. *J Pediatr Hematol Oncol*. 2002;24:69-71.