Variable Expression of HPRT Deficiency in 5 Members of a Family With the Same Mutation

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Background: Lesch-Nyhan disease is an inborn error of purine metabolism that results from deficiency of the activity of hypoxanthine phosphoribosyltransferase (HPRT). In the classic disease, the activity of the enzyme is completely deficient; the patient has mental retardation, spasticity, dystonia, and self-injurious behavior, as well as elevated concentrations of uric acid in blood and urine and its consequences of nephropathy, urinary tract calculi, and tophaceous gout. The HPRT gene is located on the X chromosome, and its expression is usually X-linked recessive. There are variant HPRT enzymes with some activity, and milder clinical expression, but the rule has been that each mutation produces a stereotypical pattern of clinical disease.

Objective: To document a family in which a single mutation has led to 3 different phenotypes in 5 individuals.

Design: Case reports.

Complete deficiency of the activity of hypoxanthine phosphoribosyltransferase (HPRT) is expected to lead to the classic phenotype of Lesch-Nyhan disease. All patients with HPRT deficiency have hyperuricemia and hyperuricosuria and are at risk for nephropathy, urinary tract stone disease, gouty arthritis, and tophaceous deposits. Those with the Lesch-Nyhan phenotype also have an impressive neurologic disorder and unusual self-mutilating behavior; this is the most common clinical picture of HPRT deficiency. It results regularly from major disruptions of the HPRT gene (OMIM 308000) such as deletions, insertions, and stop codons, but it is also the most common consequence of single nucleotide substitutions.

Missense mutations that are more conservative lead to variant enzyme proteins with varying amounts of partial activity and to 2 phenotypes that correlate moderately well with amounts of enzyme activity found on assay in an intact cell system. Those with the greatest amounts of activity display hyperuricemia and gout or urinary tract stone disease without neurologic or behavioral abnormality. An intermediate group we have called “neurologic variants” appear neurologically identical to patients with classic Lesch-Nyhan disease, but intelligence is normal or near normal, and there are no abnormalities of behavior. A unique phenotype of mild mental retardation and spasticity was observed in 4 members of a family with HPRT_Salamanca.

In the published literature, members of a family in which a mutation has been found have had a virtually identical phenotype. The purpose of this article is to describe a family (Figure) in which each affected member had the same mutation, yet the clinical phenotypes fell into 3 distinctly different patterns ranging from the classic Lesch-Nyhan phenotype to a picture much like that of HPRT_Salamanca. The condition of 2 members of the family were intermediate in severity. The 4 cousins presented in decreasing order of severity from the classic Lesch-Nyhan phenotype in patient 1 to the nearly normal appearance of patient 4.

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REPORT OF CASES

Family History

An uncle (III-3) of patients 1 and 4 (IV-1 and IV-2, respectively) died at 51 years of age. He had not been diagnosed with HPRT deficiency specifically, but his sister (III-2) said that he had presented in an identical fashion to that of patient 4 (IV-2), and that, in the last year of his life, walking became increasingly difficult.

Patient 1 (cousin IV-1 in the Figure) was seen at 32 years of age. He was born weighing 3250 g following an uneventful pregnancy and delivery. At 1 month of age he displayed poor head control and experienced difficulties with breastfeeding. At 3 months of age he was hospitalized to evaluate delayed development. By 12 months of age he was judged to have spasticity. For the next 10 years he received physical therapy because of an inability to walk. At 14 years of age he had surgery for tendon release. At 15 years of age he bit a thermometer, and at 18 years of age he bit a thermometer and broke the glass with his teeth. At 19 years of age he began biting people. He was 20 years of age when he began self-injurious behavior, predominantly biting.

Shortly thereafter he was hospitalized because of renal stones. The concentrations of uric acid and creatinine were elevated. A clinical diagnosis of Lesch-Nyhan disease was made, and treatment was initiated with allopurinol. Among his self-injurious behaviors were impulsively throwing himself forward when sitting, producing wounds on his chin, and putting his hands in boiling water. He was reported to pinch and bite relatives and caregivers, to spit at people, and to use unacceptable words.

On examination he was dystonic and wheelchair bound. His position of choice was with his head on his right shoulder, his left arm flexed at the elbow, and his wrist flexed and everted, providing a relatively constant dystonic appearance. Voluntary dystonic movement appeared with motor intention and excitement. Muscular tone was increased and reflexes, when obtainable, were accentuated. His ears were large and protruding. There was evidence of self-injurious behavior of the fingers.

Ultrasound examination of the kidneys revealed no calculi, but there were crystalline deposits in the papillary area of the kidneys.

Patient 2 (cousin IV-8 in the Figure) was seen at 24 years of age. He had been born at term following a normal pregnancy and delivery. Soon after birth he appeared anuric, but this resolved with fluid therapy. By 6 months of age he was observed to have poor head control. An acute episode of vomiting was followed by a seizure. By 18 months of age he was said to be walking but never steady. Speech developed but was never clear. At 3 years of age he developed acute renal insufficiency. Inability to produce urine, along with azotemia, led to 13 days in the hospital. Therapy with allopurinol was begun. Thereafter, there were no renal problems, although levels of uric acid remained high. At 6 years of age he began school in a special education program. He finished elementary school and learned to write with a computer. Beginning at 13 years of age he had repeated falls and many wounds on his chin. At 25 years of age he began to use a wheelchair when outside the home. In the house, he used a walker. Self-injurious behavior was denied.

On examination he was mildly dystonic but this increased with motor intention accompanied by facial grimacing and posturing of the hands. He was able to walk a bit holding onto parallel bars. Muscle tone was increased and deep tendon reflexes were accentuated.

Patient 3 (cousin IV-7 in the Figure) was seen at 31 years of age. He was born after a normal 9 months' pregnancy and a normal delivery. By 6 months of age it was clear that he had poor head control. Occasional vomiting occurred during the first year. By 18 months of age he began walking but was unsteady. Dysarthric speech began shortly thereafter. Between 2 and 8 years of age, febrile episodes led to seizures, but thereafter these did not recur, possibly because of treatment with lorazepam and levetiracetam. At 6 years of age he began school in a special education program and completed elementary school. Treatment with allopurinol began after that of his brother (IV-8). Uric acid concentration was thereafter said to be normal. He too had many falls, with injuries to his chin. He used a wheelchair when outside the home. In the house, he used a walker.

He never developed renal calculi, but often had urinary sand. At age 29 he began to display impulsive behavior, such as throwing a plate on the floor. He indicated that he was sorry for this behavior.

On examination he was mildly dystonic, which was confined to hand posturing with motor intention. He could walk well between parallel bars. Gait was spastic. Muscle tone was increased and deep tendon reflexes were accentuated.

Patient 4 (cousin IV-2 in the Figure) was seen at 29 years of age. He was born weighing 3700 g after an uneventful pregnancy and delivery. When he began walking at 13 months of age, it appeared to be on tiptoe. Talking began in the same year. Physiotherapy was begun at 2 years of age to improve his walking, and at 4 years of age surgery was performed for tendon release. He finished high school and was employed as a secretary. He was reported to have a normal IQ. A teenage attack of gout was followed by treatment with allopurinol. He complained of frequent urinary urgency, but ultrasound revealed no urinary calculi, and renal function was normal. Uric acid concentration was recorded as 5.7 mg/dL.

In the past 3 years he noted episodes of opisthotonos posturing. Legs were increasingly spastic. There was no self-injurious or impulsive behavior.
On examination he appeared normal. Speech was readily intelligible and of normal syntax and cadence. He walked without assistance with a spastic gait. Muscles were hypertonic, but there was no increase of tone with passive motion. Deep tendon reflexes were increased.

**FAMILY HISTORY**

An uncle (III-3) of IV-1 and IV-2 died at 51 years of age. He had not been diagnosed with Lesch-Nyhan disease specifically, but his sister (IV-1) said that he had presented in an identical fashion to that of III-2, and that in the last year of his life walking became increasingly difficult.

**PROCEDURES**

Activity of HPRT was assayed by modification of the method reported by Page et al. The substrate was 14C-hypoxanthine in a 100µM concentration. Venous blood was drawn and spotted on filter paper to promote stability in transport. A 3-mm hole puncher was used to produce circular pieces of blood spots, and placed in 1.5-mL Eppendorf tubes to each of which 30 µL of HEPES buffer was added. After 30 minutes at room temperature, 10 µL of phosphoribosylpyrophosphate was added, followed by 10 µL of hypoxanthine. Tubes were vortexed and placed in a 37°C water bath for 10 minutes, after which the reaction was terminated by adding 10 µL of 4.2 perchloric acid while placing the tubes on ice. After neutralization and centrifugation, supernatant fluids were spotted on a polyethyleneimine-cellulose plate. After chromatography for 1 hour, the origins were cut out, added to scintillation vials, and quantified in a liquid scintillation counter. Activities were calculated in nanomoles per hour per blood spot. The adenine phosphoribosyltransferase activity was assayed as a control.

**RESULTS**

The HPRT activity in the 4 affected cousins ranged from 0 to 0.10 nmol/h per blood spot. The control range was 11.20 to 21.40, and the level in the unaffected sibling (IV-8) was 9.60. The values in the affected patients did not differ from zero.

The mutation was a splice-site mutation (IVS6 + 21→C) that led to the exclusion of exon 6 in the HPRT gene as confirmed by the study RNA and a consequent frame shift.

**COMMENT**

An assumption has developed regarding mutations in the HPRT gene, which anticipates that individual members of a family sharing the same genetic mutation will exhibit identical phenotypes. A mutation specifying a partial variant in 1 member of a family appears similarly in other affected members, while the classic Lesch-Nyhan phenotype in a family member can be expected to appear in other affected family members for several generations. Of course there has been some variation in the appearance of self-injurious behavior, and there have been rare examples in which 1 member of a family did not display the behavior while all other affected members did. However, the rule has been for phenotypic identity within family members sharing a mutation. For example, the unusual and previously unique phenotype of HPRTaLamancawas present in multiple affected members for 3 generations.

The family described in this study represents an important exception to the rule. The 5 affected members

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**Table. Primers and PCR Conditions**

<table>
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<th>Primers</th>
<th>Sequence</th>
<th>Melting Temperature</th>
<th>Annealing Temperature, °</th>
<th>Fragment Size</th>
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<tr>
<td>HPRT 1F</td>
<td>CCTCCCTGAGCACTGAGC</td>
<td>53.8</td>
<td>62</td>
<td>229</td>
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Abbreviations: F, forward; PCR, polymerase chain reaction; R, reverse.
fell into 3 differing phenotypes; of those, 1 displayed the classic Lesch-Nyhan phenotype, 2 were very similar neurologically to that of HPRT-Salamanca although intelligence appeared to be higher, and 2 had an intermediate phenotype.

The reason for this unusual variation has not been established. The fact that the mutation causes a frameshift has led to the hypothesis that the differences in ultimate expression result from variable transcription in which varying amounts of normal and abnormal transcripts are produced.

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Author Contributions: Dr Nyhan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Nyhan. Acquisition of data: Hladnik, Nyhan, and Bertelli. Analysis and interpretation of data: Nyhan. Drafting of the manuscript: Hladnik, Nyhan, and Bertelli. Critical revision of the manuscript for important intellectual content: Nyhan. Administrative, technical, and material support: Nyhan. Study supervision: Nyhan.

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Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

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