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Nyhan, William L

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INHERITED HYPERURICEMIC DISORDERS

by

William L. Nyhan M.D., Ph.D.

University of California, San Diego
La Jolla, California
U.S.

Running Head: Inherited Hyperuricemia

Address: Dept Pediatrics 0830
University of California San Diego
9500 Gilman Dr.
La Jolla, CA 92093 US
Phone: 619 543 5337
Fax: 619 543 3565
Email: wnyhan@ucsd.edu

ABSTRACT

Inherited hyperuricemic disorders fall into two major classes, metabolic overproduction of purines and renal tubular undersecretion. The aim was to explore both. Methodology was a combination of personal experience and review of relevant literature. The overproduction hyperuricemias result from deficiency of HPRT overactivity of PRPP synthetase and deficiency of glucose-6-phosphatase. The undersecretion disorders are autosomal dominantly inherited and are heterogeneous. A major number of these patients result from mutations in the gene that codes for uromodulin. Treatment is with allopurinol.

Lesch-Nyhan Disease

Lesch-Nyhan Disease is an X-linked disorder of purine metabolism, caused by an almost complete deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT) (Fig 1). First described as a syndrome in 1964 [1, 2], it is the most common of the inherited disorders of purine metabolism and the most common cause of hyperuricemia in infancy and childhood. HPRT catalyses the recycling reaction in which the free purine bases hypoxanthine and guanine are reutilized to form their respective nucleotides, inosinic and guanylic acids. This purine salvage mechanism provides an alternative and more economical pathway to *de novo* purine nucleotide synthesis. Uric acid is the end product of purine metabolism. In the absence of the salvage pathway, excessive amounts of uric acid are produced.

The molecular defect is the virtually complete absence of activity of the HPRT enzyme [3]. The disease is usually fully recessive expressing only in males but a small number of females with the classic phenotype has been identified, predominantly reflecting nonrandom inactivation of the normal X chromosome [4]. The disease frequency approximates one in 380,000 births [5]. The gene was cloned in 1982 by Friedmann, Jolly and colleagues [6]. A large number of mutations has been defined [7].

Clinical Characteristics

Infants with Lesch-Nyhan disease appear normal at birth and usually develop normally for the first 6 to 8 months. The first manifestation is usually a consequence of

hyperuricemia, the occurrence of large quantities of what appears to be orange sand in the diaper. Unaccountably this is usually ignored until developmental delay becomes obvious, or often much later the onset of self-injurious behavior.

Ultimately these patients develop dystonia, choreoathetosis, spasticity, hyperreflexia and extensor plantar reflexes. The overall motor defect is of such severity that patients can neither stand nor sit unassisted. No patient with this disease has learned to walk. Caregivers learn to secure the patient at waist and chest which permits wheelchair mobility and participation in the world around him (Fig 2). Most patients are cognitively impaired, but mental retardation is difficult to assess because of the behavioral disturbance and motor deficits. Many patients learn to speak, but ataxic dysarthria makes their speech difficult to understand.

Self-injurious behavior is the hallmark of the disease, and occurs in 100% of patients with the classic disease. The most characteristic feature is self-destructive biting of hands, fingers, lips, and cheeks.

Hyperuricemia and Its Consequences

Hyperuricemia is present in almost all patients. Levels usually range from 5 to 10mg/dl. Occasionally a very efficient renal excretor is found in whom the level is normal. Thus, the plasma uric acid is not an appropriate way to exclude metabolic uric acid overproduction. The excretion of uric acid is 3 to 4 mg of uric acid per mg creatinine (1.9 ± 0.9 mmol/mol creatinine) [8]. Normal children excrete less than 1 mg uric acid/mg creatinine. The consistent finding of this elevated uric acid to creatinine ratio and its relative ease of measurement usually make it a useful initial

screening test for this and other metabolic hyperuricemic disease [8]. Urinary data for uric acid can be spuriously low as a result of bacterial contamination and 24 hour collections at room temperature are especially suspect. The clinical results of the accumulation of large amounts of uric acid in body fluids are the classical manifestations of gout.

Biochemical and Molecular Features

HPRT (EC 2.4.2.8) is a cytoplasmic enzyme expressed in every cell of the body. Highest levels are found in the basal ganglia and testis. The defect is detectable in erythrocyte hemolysates and in cultured fibroblasts. It is most readily measured in red cell lysates in which quantitative assays yield virtual zero activity [9].

The HPRT gene is located on the long gene arm of chromosome X (Xq26-q37). The sequence of the gene spans more than 44 kb; the coding region consists of 654 nucleotides in 9 exons. The protein contains 218 amino acids. Characterization of the molecular defect in the HPRT gene of a number of HPRT-deficient patients has revealed a heterogeneous pattern of mutations, with the same alteration rarely being found in unrelated pedigrees [7]. About 63% of described molecular alterations represent point mutations which yield amino acid substitution in the protein sequence or stop codons which lead to truncated proteins. In some instances a point mutation alters a splice site consensus sequence, activating an alternative, cryptic splice site, creating aberrant mRNA and protein products. Genotype/phenotype correlations have been elusive, but major mutations that completely disrupt HPRT enzyme function (stop codons, deletions, or insertions) are usually associated with the classical Lesch-Nyhan phenotype, while

variant HPRT phenotypes (v.i) are found in patients with point mutations, usually conservative amino acid substitutions.

Treatment

The excessive uric acid production in HPRT-deficient patients is effectively treated with daily administration of allopurinol. This is the unique and specific treatment available for all the patients diagnosed with HPRT deficiency, both classical Lesch-Nyhan and variants. Unfortunately, no medication has been found to be consistently effective in treating the neurological or behavioral manifestations of the disease in classical Lesch-Nyhan patients. The only successful approaches to the self-injurious behavior have been physical restraint and the removal of teeth, to prevent self-biting. Future approaches may include gene therapy; promising results have already been obtained *in vitro*.

HPRT Variants

Following the recognition that the defect in Lesch-Nyhan disease was in HPRT, enzyme deficient was found in patients with gout [10] and with urinary tract calculi [11]. Initially it was thought that this population of patients with HPRT deficiency might be quite large, but this is not the case. Most patients with HPRT deficiency have Lesch-Nyhan disease, and most patients with gout do not have HPRT deficiency. Of course, most patients with gout do not have overproduction of purines, or increased urinary excretion of uric acid, but even among those that do, HPRT deficiency is not frequently encountered. Nevertheless, a specific diagnosis is always to be desired, and in this

situation it can influence not only therapy but the genetic evaluation of the family. Any patient with gout should be studied for the possibility of increased excretion of uric acid, because the treatment of such a patient with a uricosuric agent such as probenecid can induce fatal renal shutdown. Assay for HPRT deficiency should be undertaken in any patient with overproduction hyperuricemia. The enzyme should also be assayed in any patient with uric acid calculi. In an infant or child with renal stones, it may be easier to obtain an assay of HPRT than of the nature of the calculus, especially since so many calculi are lost.

Some variant enzymes display some residual activity in the erythrocyte assay, often more than 5% of control, making them readily distinguishable from the classic Lesch-Nyhan pattern, a distinction that is particularly important in assessing prognosis in a newly diagnosed young infant. These patients have been referred to as partial variants (Table 1). However many patients with variant clinical phenotypes have zero activity in the erythrocyte assay, and such patients also display no activity in fibroblast lysates.

Distinctions among variants became possible with the development of methodology for the assessment of enzyme assay in intact cultured fibroblasts [12]. This assay remains the gold standard for the distinction of classic Lesch-Nyhan patients from variants. There is a rough inverse relationship between the severity of clinical manifestations and the amount of residual activity observed in the intact cell assay [12]. To carry out the assay cultured fibroblasts are incubated with ^{14}C -hypoxanthine, the products are separated by high performance liquid chromatography, and the total number of picomoles of isotope incorporated into purine compounds is expressed per nanomole of total purine compounds. The method permits the assessment of the kinetic properties

of HPRT. The K_m for hypoxanthine found in normal fibroblasts was identical to that of the purified human enzyme, and a number of kinetic variants has been reported [13]. Patients with Lesch-Nyhan have displayed activity below 1.5% of normal and the classic partial variants all had greater than 8% of control activity.

The phenotype of patients with these partial variants of enzyme consists of manifestations that can be directly related to the accumulation of uric acid in body fluids, acute attacks of gouty arthritis, tophi, and renal and urinary tract complications. The central nervous system and the behavior are normal.

To these two populations of HPRT deficient patients, the classic Lesch-Nyhan variants and the classic partial variants, it became evident that there was a third group, and these patients had an intermediate level of enzyme activity in the whole cell assay. We have called these intermediate patients neurologic variants (Table 1). This small but important group of patients is usually characterized by a neurological phenotype that is identical to that of the classic Lesch-Nyhan patient with spasticity dystonia and choreo-atheosis. They are confined to wheelchairs and unable to walk. However, behavior is normal and intelligence is normal or nearly normal. Among the variants studied one patient with a classic Lesch-Nyhan phenotype and 1.4% of control activity could be distinguished from other Lesch-Nyhan variants by the more normal behavior of his cells in selective media [14].

Another phenotype with 7.5% of residual activity in the intact cell assay and a different neurologic picture was observed in a family whose HPRT variant we have called HPRT_{Salamanca} [15]. Four males in three generations had an identical phenotype, the most prominent feature of which was spastic diplegia. They all could walk, but gait was

classically spastic. Hypertonicity and brisk deep tendon reflexes were more prominent in the lower extremity. Babinski responses were positive bilaterally. There was bilateral pes cavus and exaggerated lumbar lordosis. Mental retardation was mild. Tophaceous gout appeared by 32 years in a previously untreated patient.

In variant patients missense mutations have been the rule, and the changes have been conservative. In the original patient of Catel and Schmidt [16, 17] the mutation changed a valine to a glycine [18], which would not be expected to make a major difference in protein structure. Others had changes such as an isoleucine to a threonine. In these patients and in the partial or hyperuricemic variants no deletions, stop codons or major rearrangements were observed. In HPRT_{Salamanca} there were two mutations: a T-to-G change at position 128 and a G-to-A at 130. These changes resulted in the substitution of two adjacent amino acids at position 43 and 44: methionine to arginine and aspartic acid to asparagine. These would not appear to be particularly nonconservative, but the phenotype was probably the mildest of the neurologic variants observed. They may have reflected another observation, that the milder mutations have tended to cluster at the amino terminal end of the enzyme. Point mutations in Lesch-Nyhan patients have been more likely to be sited in areas important to substrate binding and catalytic activity.

Phosphoribosylpyrophosphate Synthetase Overactivity

Mutant phosphoribosylpyrophosphate (PRPP) synthetase in which activity is greater than normal leads to a syndrome of hyperuricemia and uricosuria [19]. The expected complications include hematuria, crystalluria, urinary tract calculi, nephropathy and gouty arthritis. In some kindred's there has been sensorineural deafness [20, 21].

Clinical Characteristics

In this disease hyperuricemia and uricosuria are invariant. Any of the clinical consequences of the accumulation of uric acid in body fluids may result. Gouty arthritis has been reported with onset as early as 21 years of age [19]. Renal colic has been observed, as well as the passage of calculi [22]. One boy developed hematuria at the age of 2 months and was found to have crystalluria, hyperuricemia and uricosuria [23]. In families in which clinical onset is early females may develop symptoms prior to menopause [24].

Deafness in some families has been associated with severe neurodevelopmental retardation [21]. One of our patients [20] was thought to be mentally retarded, and his behavior was thought to be autistic, but with time it was apparent that he was deaf, and his behavior was quite appropriate.

Hyperuricemia and its Consequences

Increased amounts of uric acid in the blood and urine are the rule, and concentrations in serum may range from 8 to 12mg/dl [19, 20]. In the initial proband [19] uric acid excretion was 2400mg per 24hr. Urinary excretion may range from 1.8 to 3.3mg/mg creatinine. Overproduction of purine de novo has been documented by measuring the in vivo in conversion of ^{14}C -glycine to urinary uric acid [20].

The enzyme defect is an altered PRPP synthetase structure which leads to superactive enzyme activity. Activity may be three times that of the normal enzyme [22-24]. The amounts of immunoreactive enzyme protein may be normal. These observations indicate the presence in normal amounts of a protein in which structural alteration leads

to increased specific activity. The data are consistent with the presence of two important sites on the enzyme: a catalytic site which may be altered by mutation and a regulatory site which may be altered by another, or altered structure may affected both catalytic and regulatory activities [25].

The altered PRPP synthetase, though hyperactive, may also be unstable. Diminished levels in old erythrocytes may be low or normal. Therefore enzyme assay of erythrocyte lysates in this disease may be misleading [25].

Intact cultured fibroblasts in this disease incorporate purines, adenine, guanine and hypoxanthine, more rapidly into nucleotides than do controls [25], and incorporation of ^{14}C labeled formate is also accelerated. These findings indicate the presence of increased intracellular concentrations of PRPP, and this may be the most reliable method of screening for the disease.

Biochemical and Molecular Features

PRPP synthetase (EC 2.7.6.2) catalyzes the initial step in the de novo synthesis of purines in which ribose-5-P reacts with ATP to form PRPP. PRPP is the substrate for the first rate-limiting step in the 10-step reaction. Increased quantities of intracellular PRPP lead to overproduction of purine de novo and of uric acid which ultimately yields IMP. PRPP synthetase is coded for by two genes on the X chromosome at Xq 22-24 and Xp22.2-22.3 [26]. The genes have been cloned and sequenced [27] and referred to as PRPS1 and S2. A small number of point mutations have been defined in PRPS1 in patients with overactivity and altered allosteric properties of the enzyme. In 6 patients with overactivity of PRPP synthetase no mutations in the cDNA of PRPS1 or S2 were found; instead there were increased quantities of the S1 isoform whose physical and catalytic properties were normal [28].

The S1 isoform of PRPP synthetase, while coded for by a gene on the long arm of the X chromosome [28] may be fully recessive or may be expressed in the heterozygous female. This could reflect different degrees of lyonization. On the other hand, it is easier

for an overactive enzyme than the more common deficient one encountered in inborn errors to function as an X-linked dominant.

Treatment

Allopurinol is the treatment of choice in any overproduction hyperuricemia including the PRPP synthetase defects. Treatment of abnormalities in PRPP synthetase is simpler than that of HPRT deficiency because in the presence of normal HPRT activity there is extensive reutilization of hypoxanthine accumulating behind the block in xanthine oxidase, leading to a substantial decrease in the overall excretion of oxypurines in the urine. In contrast, in HPRT deficiency there is simple substitution of hypoxanthine or xanthine for uric acid, and the total oxypurine excretion does not change. Hearing should be tested promptly and appropriate intervention provided.

Glycogen Storage Diseases

Hyperuricemia and typical clinical gout occur in teenagers and adults with glycogenosis type I (Von Gierke disease) due to defective activity of glucose-6-phosphatase [29]. The mechanisms responsible for the hyperuricemia include overproduction of purine *de novo* [29], but also diminished clearance of uric acid resulting from competition for tubular secretion by lactic acid, 3-hydroxybutyric acid and acetoacetic acid [30].

Hyperuricemia may also be encountered in Type III glycogenosis in which there may be clinical myopathy, as well as in Type V and Type VII, but these patients do not have gout. The mechanism is abnormal metabolism of glycogen in muscle, in which carbohydrate substrates are inadequate for ATP synthesis, and its breakdown leads to purine excess and conversion to uric acid [31].

Clinical Characteristics

In classic type Ia glycogen storage disease symptoms the disease may be recognized at birth. Neonatal hypoglycemia is a major manifestation. Hepatomegaly is usually at birth and progresses to huge enlargement of the liver without splenomegaly. Many infants present with vomiting or convulsions in the morning. In addition to the hypoglycemia a variety of chemical abnormalities are classic. Lactic acidemia is a regular feature of the disease. Marked hyperlipidemia and hypercholesterolemia are also features. The hyperlipidemia leads not only to the formation of xanthomas, but also to large lipid-laden reticuloendothelial cells in the bone marrow. The plasma may be milky. Ketosis and ketonuria occur promptly with minimal degrees of fasting. This and the lactic acidosis concomitantly may lead to metabolic acidosis. Hyperuricemia is present from infancy, but clinical gout does not appear until adolescence [29]. Decreased clearance of uric acid has does not occur in all patients [32]. Studies of uric acid production have indicated increased purine synthesis in this disease [29, 33, 34].

Chronic renal tubular and glomerular disease are late complications of glycogenosis I. They are independent of the hyperuricemia.

Biochemical and Molecular Features

The molecular defect in glycogenosis I is defective activity of glucose-6-phosphatase. The enzyme is normally expressed only in liver, kidney and in the β cells of pancreatic islets. The diagnosis is usually made by assay of biopsied liver.

The cDNA for human hepatic glucose-6-phosphatase has been cloned and a number of mutations has been identified [35]. These include an arginine-to-cysteine change at amino acid 83 (R83C) and Q347X. Assay for common mutations permits diagnosis without liver biopsy.

Treatment

Allopurinol is the treatment of choice for the hyperuricemia.

Renal Hyperuricemia

Among adults with gout, the mechanism for hyperuricemia is not overproduction, but diminished renal excretion of uric acid in at least 80% of patients [36]. This may be described as excretion of less than 250-300mg of uric acid by a hyperuricemic adult ingesting a purine-free diet. Renal clearances of uric acid are low. The mechanism appears to be diminished renal tubular secretion of uric acid [37, 38, 39, 40]. Decreased secretion may be demonstrated by the response to the uricosuric drug benzbromarone, which inhibits reabsorption of secreted uric acid.

Uric acid is filtered freely at the glomerulus, and nearly all is reabsorbed before the distal convoluted tubule. The majority of the uric acid in the urine is the result of

secretion. Secretion and post secretory reabsorption are thought to occur in the proximal tubule. The minimal rate of tubular secretion of uric acid has traditionally been assessed by determining the response to pyrazinamide (PZA). Its product pyrazinoic acid inhibits uric acid excretion [41]. In a family with dominantly inherited hyperuricemia and gout we observed normal responses to PZA [42]. These patients had a brisk uricosuric response to probenecid, suggesting that the mechanism for decreased excretion of uric acid in these families was enhanced tubular reabsorption of uric acid. Gutman and colleagues [43] were also unable to identify defective tubular secretion in a series of patients with gout.

Clinical Characteristics

Patients with renal hyperuricemia have all of the clinical consequences of hyperuricemia including tophaceous gout, renal calculi and urate nephropathy [42]. Genetic transmission is autosomal dominant.

A syndrome of familial juvenile hyperuricemic nephropathy (FJHN [MIM 162000]) is an autosomal dominant disorder in which abnormal renal tubular excretion of uric acid and gout are associated with the late development of interstitial nephritis and progressive renal failure [44, 45, 46].

Biochemical and Molecular Features

An interesting new mechanism for hyperuricemia has been recently discovered in FJHN [45, 46]. It is to pathologic findings in FJHN raised similarities with autosomal dominant medullary cystic kidney disease (MCKD [MIM 174000]). MCKD was mapped

to chromosome 16p12 in an Italian family [47]. This was then designated MCKD₂ (MIM 603860) and the MCKD linked to chromosome 1q21, MCKD₁. FJHN was then linked to 16p12 in a Belgian family [48], and Hart et al. [49] found the gene for FJHN and identified a number of mutations. The gene has been designated *UMOD*, because it codes for uromodulin protein, and this is the same as the Tamm-Horsfall protein, the most abundant protein in normal urine and a major component of urinary casts; it was originally characterized as an inhibitor of viral hemagglutination.

In patients with FJHN a number of mutations has been identified in *UMOD*, most of them missense. Apparently they code for uromodulin proteins which are not found in the urine; rather they accumulate in renal tubules, which become dilated, distorted and cystic, the appearance of MCKD. A common mechanism has been discovered for the hyperuricemia and for the nephropathy. Mutations in *UMOD* appear to be the most common cause of FJHN [46]; it is also clear that there are other causes of FJHN, and that MCKD₁ is a different disease.

The gene for the urate-anion exchanger integral to the proximal tubular reabsorption of uric acid has been identified as *URAT1*. Mutations in this gene on chromosome 11p13 have been identified, and they cause uricosuria and hypouricemia [50, 51].

Treatment

Allopurinol remains the drug of choice.

ILLUSTRATIONS

Figure 1. The hypoxanthine-guanine phosphoribosyl transferase (HPRT) reaction.

This enzyme is the molecular defect in the Lesch-Nyhan disease.

Abbreviations include GMP, guanylic acid; and IMP, inosinic acid.

Figure 2. A patient with the Lesch-Nyhan disease illustrating the loss of tissue about the mouth that resulted from biting.

Figure 3. Tophaceous gout in a 24 year old with previously undiagnosed Lesch-Nyhan disease [14]. He came to clinical attention and diagnosis after developing septicemia following the breakdown of the skin over tophaceous deposits about the knee.

Table 1
Spectrum of Deficiency of HPRT

Features	HPRT Activity	Clinical
Classic LN Disease	Virtually 0 under any conditions	Lesch-Nyhan syndrome
Neurological Variants choreoathetosis, hyperuricemic	Essentially 0 in Rbc assay Unstable or altered kinetics 1.5-8% activity in intact cell assay	Spasticity, good mental functions, normal behavior, manifestations
Partial Variants	0-50% in Rbc assay. >8% complications Neurologically normal	Gout or nephrologic co activity in intact cell assay

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