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Update on the Phenotypic Spectrum of Lesch-Nyhan Disease and its Attenuated Variants

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Abstract

Congenital deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) results in a spectrum of clinical phenotypes. All of these phenotypes are associated with marked overproduction of uric acid and related problems such as hyperuricemia, urate nephrolithiasis, tophi, and gout. The mildest phenotypes include only problems related to overproduction of uric acid. The most severe phenotype is known as Lesch-Nyhan disease, in which the phenotype also includes severe motor handicap, intellectual disability, and self-injurious behavior. In between these two extremes is a continuous spectrum of phenotypes with varying degrees of motor and cognitive handicap but no self-injurious behavior. The pathogenesis of overproduction of uric acid in HPRT deficiency is well-understood, and treatments are available to control it. The pathogenesis of the neurobehavioral problems is less well-understood, and effective treatments for them are lacking.

Keywords

Inborn errors of metabolism; Uric acid; Lesch-Nyhan disease; Phenotypic spectrum; Gout; Nephrolithiasis; Treatment; Variants; Crystal arthritis

Introduction

Lesch-Nyhan disease (LND) is one of several monogenic disorders with a high risk of the development of gout due to a metabolic defect that is associated with marked overproduction of uric acid [1, 2]. The classical clinical phenotype includes overproduction of uric acid, severe motor handicap resembling dystonic cerebral palsy, intellectual disability, and recurrent self-injurious behaviors. Since its original description in 1964 [3], there has been increasing appreciation of attenuated clinical phenotypes wherein some of the features of the classical phenotype are absent or sufficiently mild that they escape clinical detection.

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The pathogenic processes leading to overproduction of uric acid and its consequences are now well-understood, and effective treatments are available to reduce the risk of gout and nephrolithiasis. The mechanisms leading to the neurological and behavioral abnormalities are only partially understood [4]. These mechanisms are likely to be unrelated to those leading to overproduction of uric acid, as control of hyperuricemia, even from birth, has no influence on the neurobehavioral aspects.

Spectrum of Clinical Manifestations

The classic form of LND evolves in a very characteristic fashion, with the majority of patients presenting with neurodevelopmental delay in the first year of life [5]. Poorly controlled movements along with increased muscle tone also emerge during the first year of life. These problems often worsen until 4 to 6 years of age, after which they appear relatively stable. Severe and recurrent self-injurious behaviors, such as self-biting or self-hitting, typically emerge between 2 and 4 years of age. However, in some cases, these difficult behaviors may be delayed until the late teenage years. Mild or moderate intellectual disability is also common, although severe mental retardation is unusual [6]. The overproduction of uric acid is present even at birth and can be detected by hyperuricemia or increased urinary uric acid excretion. It has been estimated that uric acid is produced at rates of at least 5 to 10 times that of healthy individuals [7–9]. However, the overt clinical consequences of uric acid overproduction often take time to develop, so patients with classic LND only rarely present with renal stones or gout as their initial clinical manifestation (Table 1).

In addition to the classic phenotype of LND, there are attenuated phenotypes in which some clinical features may be absent or sufficiently mild to escape clinical detection [10, 11, 12]. Classic LND is the most severe phenotype. There are intermediate phenotypes that lack self-injurious behaviours, and some of these patients may appear cognitively healthy. However, patients with the intermediate phenotypes often have some difficulty with muscle control, which may range from severe and incapacitating to only minor clumsiness or stiffness that is clinically insignificant. Patients with the intermediate phenotypes also suffer from overproduction of uric acid. The mildest phenotypes have no obvious behavioral or neurological disturbances. However, uric acid overproduction occurs in even the mildest phenotypes.

Because the behavioral and neurological manifestations are sometimes absent or very mild in the LND variants, these patients more often come to medical attention first due to complications related to uric acid, such as nephrolithiasis or gout (Table 1). Patients with the classic phenotype are easy to diagnose because the clinical syndrome is quite characteristic. The attenuated variants with milder syndromes are much more difficult to diagnose. However, the most consistent element for all phenotypes is overproduction of uric acid, and this phenomenon often provides an important clinical clue for all the phenotypes associated with the hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme deficiency. Evidence of overproduction of uric acid may come in the form of an unexplained elevation in serum uric acid, uric acid nephrolithiasis, gout, and/or tophi. Although these problems may be common in adult populations, their occurrence in children or young adults is unusual and should prompt work-up for a metabolic defect.

Some authors apply the eponym *Kelley-Seegmiller syndrome* to the LND variants, in recognition of one of the earliest descriptions of 18 patients with LND variants, only 5 of whom had neurological abnormalities [13]. However, there are several reasons to question the use of this eponym. First, its meaning has never been clearly defined. Some authors use it to refer only to the mildest expressions of the disease with overproduction of uric acid and

no significant neurological features, similar to the cases in the original report. Others apply the term to any LND variant, including those with significant neurological disability but lacking self-injurious behaviors. These disparities have led to confusion regarding the meaning of this eponym. Another reason to question the eponym is that Kelley and colleagues were not the first to describe the LND variant phenotype, although they were the first to recognize that their patients shared the same enzymatic defect as classic LND. Catel and Schmidt [14] reported the clinical features of an LND variant in the German literature before the classic syndrome was recognized. The biochemical defect in this early patient was confirmed in later studies [15, 16]. Other LND variants also were reported early in the French literature [17–20]. A third reason to question the eponym is that it appears that the neurobehavioral assessments presented by Kelley and colleagues were incomplete and in some cases inaccurate. Two cases were described as having a neurological syndrome resembling spinocerebellar ataxia, but subsequent evaluations of the same patients suggested this description was inaccurate [21]. Formal motor and neuropsychological testing was not conducted in the original study, and the extent of impairments was therefore underestimated. In fact, more recent studies of 47 LND variants revealed neurological or behavioral abnormalities in all but 2 after thorough evaluation [10••]. These findings suggest that the proposed phenotype of overproduction of uric acid alone with little or no neurobehavioral impairment is quite rare. Perhaps the strongest reason for questioning this eponym is that it has become increasingly clear that there is a continuous spectrum of neurobehavioral dysfunction in LND and its variants, ranging from very severe to clinically insignificant [10••]. It is not clear that having two eponyms for a disorder with a continuous spectrum of disease severity is useful, as it misleadingly implies the existence of distinct patient subgroups. Based on these considerations, we believe the eponym *Kelley-Seegmiller syndrome* should be dropped and replaced with the term *Lesch-Nyhan variant*.

Molecular and Metabolic Basis

LND and its variants are all caused by a defect in the *HPRT* gene, which is located on the X chromosome [22]. The disorder is inherited in an X-linked recessive fashion, so virtually all patients are male. However, female cases may occur rarely as a result of defects involving both X chromosomes. Unlike some disorders in which one or a few mutations account for disease in many patients, the mutations in LND and its variants are quite heterogeneous, with a variety of molecular defects spread across the entire *HPRT* gene. There are more than 400 mutations reported to date (<http://www.lesch-nyhan.org>). Included are point mutations leading to single amino acid substitutions, mutations leading to premature termination of protein translation, deletions, insertions, splicing mutations, and other more complex substitutions or rearrangements.

The mutations affect the coding of HPRT, a housekeeping enzyme that plays an important role in the recycling of purines. In general, mutations that result in null enzyme function are associated with the most severe phenotype of classic LND, while mutations that permit residual activity are associated with the attenuated variants. Some exceptions to this rule have been reported, although they may reflect an artifact of the assays used to measure the enzyme [23].

The mechanisms responsible for overproduction of uric acid in HPRT deficiency are best understood by knowledge of de novo purine synthesis, purine salvage, and purine degradation [24]. The de novo synthesis of purines occurs through a multistep process that consumes considerable energy. An inosine monophosphate (IMP) molecule is formed in 10 consecutive steps from phosphoribosyl pyrophosphate (PRPP) with the incorporation of formate, hydrogen carbonate, glutamine, and aspartic acid. Including PRPP synthesis, the synthesis of an IMP molecule consumes six adenosine triphosphate (ATP) molecules. The

synthesis of PRPP from ribose-5-phosphate, glycine, and ATP is catalyzed by the enzyme PRPP synthetase, and the intracellular concentration of PRPP has been shown to influence the rate of purine biosynthesis de novo. PRPP is also required for the salvage pathways of purines and for pyrimidine nucleotide synthesis. De novo purine synthesis is mainly regulated by the enzyme amidophosphoribosyltransferase, which catalyzes the first reaction of de novo purine biosynthesis, the formation of phosphoribosylamine from PRPP and glutamine. This enzyme is stimulated by increased concentrations of PRPP and is subject to feedback inhibition by the purine nucleotides IMP, adenosine monophosphate (AMP), and guanosine monophosphate (GMP).

Purine recycling in humans is mediated by three different enzymes: HPRT, adenine-phosphoribosyltransferase (APRT), and adenosine kinase. It is estimated that 90% of free purines generated in the intracellular metabolism are recycled rather than degraded or excreted [25, 26]. Purine recycling allows for more efficient functioning of purine metabolism. HPRT recycles hypoxanthine and guanine into IMP and GMP, respectively. APRT, structurally and functionally similar to HPRT, recycles free adenine into AMP. HPRT and APRT both use the cosubstrate PRPP in the recycling reaction. The incorporation of free purine bases and nucleosides from extracellular sources also helps maintain purine pools. Dietary vegetables and animal products, through digestion, generate purines following DNA and RNA degradation. Some of these compounds are absorbed from the gut and incorporated into purines by the liver. These purine bases are exported into the bloodstream to be used by other tissues. The salvage enzymes are needed to incorporate preformed purine bases into the cellular purine pool. Thus, a salvage enzyme deficiency not only results in an inability to salvage intracellular purines, but also in an inability to incorporate purines from extracellular sources.

Purine nucleotide degradation is initiated by nucleotide dephosphorylation and nucleoside formation (adenosine, inosine, and guanosine). This process is catalyzed by 5'-nucleotidases and other nonspecific phosphatases. Inosine and guanosine, through the action of purine-nucleoside phosphorylase, are then transformed into the purine bases hypoxanthine and guanine, respectively. Finally, the purine bases hypoxanthine and xanthine are oxidized to uric acid by the enzyme xanthine oxidase. Guanine, on the other hand, is converted to xanthine by guanine deaminase or guanase. In general, the activity of these enzymes in the degradative pathways is regulated by substrate availability. In humans and primates, uric acid is the final product of purine metabolism, but in other mammals, uric acid is degraded to allantoin by the enzyme uricase.

Two main enzyme defects are responsible for uric acid overproduction: PRPP synthetase overactivity and HPRT deficiency. Enhanced PRPP synthetase activity leads to an increased availability of PRPP for PRPP amidotransferase, the rate-limiting enzyme of the novo synthesis of purine nucleotides. A defect in HPRT results in the accumulation of its substrates, hypoxanthine, guanine, and PRPP. The increased availability of PRPP for PRPP amidotransferase contributes to increase de novo purine synthesis [27–29]. HPRT deficiency also leads to a presumed decrease in the PRPP amidotransferase feedback inhibitors, IMP and GMP. This dual mechanism of increased PRPP and reduced feedback inhibition results in an increased de novo synthesis of purine nucleotides. The combination of deficient recycling of purine bases with increased synthesis de novo of purine nucleotides explains the marked uric acid overproduction in HPRT deficiency.

Mechanisms Responsible for Gout

Gout is a crystal arthropathy that involves metabolic homeostasis and renal clearance of urate along with the immunologic system. The primary cause of gout is monosodium urate

crystal deposition related to hyperuricemia. Hyperuricemia may be the result of an increased synthesis of uric acid and/or inefficient excretion by the kidneys. These two possibilities have been differentiated for decades in patients with gout by measuring urinary uric acid excretion. Increased uric acid synthesis is associated with high urinary uric acid, whereas decreased excretion is associated with low urinary uric acid.

The vast majority of patients with primary gout have decreased urinary uric acid excretion. Decreased renal excretion has been related to several renal tubular urate transporter polymorphisms, including SLC2A9, ABCG2, and others [30]. In secondary gout, decreased urinary urate excretion can result from several problems, including renal failure, hypothyroidism, volume contraction and volume depletion, acidosis, lead intoxication, and familial nephropathy due to uromodulin deposits. Some drugs can also cause iatrogenic gout with urate underexcretion, including salicylic acid, diuretics, and pyrazinamide.

Gout due to uric acid overproductions is associated with hyperuricemia plus hyperuricosuria. This association can be found in several inborn errors of metabolism, including HPRT deficiency, PRPP synthetase overactivity, and glucose-6-phosphate dehydrogenase deficiency (Von Gierke disease). Purine overproduction also has been linked to high cellular turnover (hematologic and neoplastic diseases, cytostatic treatment, and psoriasis) and increased ATP catabolism (ie, ethanol; exhausting exercise and tissue ischemia; glycogen storage disease types III, V, and VII). Finally, certain dietary excesses can contribute to gout.

Monosodium urate crystals are formed when uric acid exceeds its solubility threshold in certain tissues [31]. Monosodium urate crystals tend to precipitate in joints and periarticular tissues and engage the caspase-1-activating and the NALP3 (also called cryopyrin) inflammasome, resulting in the production of active interleukin (IL)-1 β and IL-18. At the molecular level, gouty inflammation begins with phagocytic cells such as monocytes or macrophages that sense the crystals and the NALP3 inflammasome activation. The phagocytes trigger the processing and release of active IL-1 β , which binds to target cells as synoviocytes and activates inflammatory transcription factors such as nuclear factor- κ B. The production and release of inflammatory mediators such as neutrophil-recruiting chemokines follows. Resolution of the inflammation is in part due to the removal or dissolution of the crystals by phagocytes, anti-inflammatory cytokines such as transforming growth factor- β , and other mechanisms aimed at regulating IL-1 [32].

A tophus is composed of monosodium urate crystals in a matrix of lipids, protein, and mucopolysaccharides. These tend to occur in the periarticular regions of cool parts of the body such as the feet and hands, but they also occur in the cartilage of the ear. Bone with tophus has altered remodeling and cellular distribution showing bone destruction. It has been reported that neutrophils, through elastase localized at their surface, induce retraction of confluent osteoblasts, and this retraction allows osteoclasts to resorb cell-free areas of the matrix.

Treatment

The best available management of uric acid overproduction in HPRT-deficient patients is blocking the conversion of xanthine and hypoxanthine into uric acid with a xanthine oxidase inhibitor [33, 34]. Allopurinol has been the traditional choice. Uricosuric drugs are not recommended, as they can aggravate nephrolithiasis by concentrating large amounts of uric acid in the kidneys and urogenital system. Although allopurinol has no effect on neurobehavioral problems, it should be started as soon as the enzyme deficiency is diagnosed to avoid gout and renal damage. In adults, or when there are substantial tissue urate deposits, combined treatment with colchicine prophylaxis or NSAIDs is required to

avoid gout flares. The optimal allopurinol dose for HPRT-deficient patients has not been established. Despite the enormous overproduction of uric acid, doses typically used for more common forms of gout seem adequate. Recommended allopurinol doses most commonly begin at 5 to 10 mg/kg daily, with final total doses ranging from 50 to 600 mg/d. Allopurinol resistance appears to be uncommon, and patients who seem to respond poorly should raise concerns regarding medication noncompliance. In our experience, treatment with allopurinol results in a mean reduction of about 50% in serum urate and a 74% reduction in urinary uric acid/creatinine ratio.

In LND and its variants, inhibition of xanthine oxidase increases baseline hypoxanthine and xanthine urinary excretion about fivefold and 10-fold, respectively [7, 8]. In normal conditions, allopurinol increases HPRT-mediated recycling of hypoxanthine for nucleotide synthesis. The resultant increase in nucleotide concentration leads to feedback inhibition of de novo purine synthesis. However, in HPRT-deficient patients, hypoxanthine cannot be reutilized, and purine synthesis is upregulated. As a result, hypoxanthine levels increase and concentrations of xanthine may rise to a level exceeding its solubility, causing xanthine lithiasis. A frequent error in the management of nephrolithiasis in LND and its variants is to assume all stones forming during therapy are composed of uric acid. This assumption leads to a further increase in the allopurinol dose to prevent them [35, 36]. However, if the stones are composed of xanthine, this strategy will aggravate stone formation, and a better approach would be to lower allopurinol doses. When stones unexpectedly form during therapy, they should be collected and chemically examined. Therapy can be adjusted according to whether the stones are comprised of uric acid, xanthine, or other oxypurines.

The inhibition of xanthine oxidase with allopurinol should be accompanied by adequate hydration to avoid urinary crystal precipitation. Urinary alkalinization has been advocated to minimize the formation of uric acid stones, as uric acid is more soluble in alkaline environments [37, 38]. Uric acid is a weak acid with a pK_a of 5.75. At a physiologic pH of 7.40 in the extracellular compartment, 98% of uric acid is in the ionized form as a monosodium urate salt. In the collecting tubules of the kidneys, where pH may drop below 5.75, the predominant form is nonionized uric acid. The solubility of monosodium urate is about 18 times greater than that of uric acid in aqueous solutions. This solubility difference provides the therapeutic rationale for alkalinization of the urine pH above 6.0. Although urinary alkalinization is widely employed, its efficacy has never been formally examined.

Although xanthine calculi typically develop in acidic urine, they are less responsive to urinary alkalinization. The pK_a of xanthine is 7.4. A solubility threshold of 5 mg/dL at a pH of 5 rises to only 13 mg/dL at a pH of 7. Therefore, pH changes have only a minor influence on xanthine stone solubility. Because xanthine stones are far more difficult to dissolve than uric acid stones, we recommend titrating allopurinol doses to maintain high-normal serum uric acid levels and a urinary uric acid/creatinine ratio lower than 1.0. In our experience, when serum urate is maintained only slightly below its solubility threshold, urate deposition does not occur and xanthine lithiasis may be avoided. With strict compliance and careful monitoring of allopurinol, renal function usually remains stable or even improves.

Allopurinol hypersensitivity has been described in 0.4% of patients. The higher incidence of hypersensitivity in patients with decreased renal function has prompted adjustment of allopurinol doses according to creatinine clearance. However, this procedure does not always prevent the allopurinol hypersensitivity. To our knowledge, no hypersensitivity reaction has been described in HPRT-deficient patients despite an impaired renal function.

Febuxostat is a novel non-purine inhibitor recently marketed for hyperuricemia and gout treatment [39]. Febuxostat is a potent inhibitor of the oxidized and reduced forms of the

enzyme xanthine oxidase, whereas allopurinol and its active metabolite, oxypurinol, inhibit only one form of the enzyme. This difference has been postulated to account for the higher potency and long-lasting action of febuxostat. On the other hand, contrary to allopurinol, febuxostat is not a substrate of purine and pyrimidine metabolic enzymes, such as HPRT or orotate phosphoribosyltransferase, and does not inhibit purine nucleoside phosphorylase and orotidine-5'-monophosphate decarboxylase. Febuxostat is not routinely employed in HPRT-deficient patients, but it could be an alternative if allopurinol cannot be used.

In most mammals the hepatic enzyme uricase or urate oxidase transforms uric acid to a more soluble compound, allantoin. In humans, due to a mutation in the uricase gene, uric acid is the last product of purine metabolism. Rasburicase, an uricase purified from *Aspergillus flavus*, is employed to prevent problems related to overproduction of uric acid associated with the tumor lysis syndrome in hematologic malignancies. It is administered intravenously at doses of 0.20 mg/kg per day during a short period of 5 to 7 days. In principle, xanthine lithiasis in HPRT-deficient patients similarly could be avoided by uricase treatment. However, no long-term data are available regarding the safety of rasburicase, and it is known to be antigenic. Its short half-life (18 hours) and its intravenous means of administration render it inconvenient for chronic therapy. However, rasburicase may be effective in infants with acute kidney injury. Two of our LND patients who presented with renal failure in the first months of life were treated transiently with rasburicase at established doses, followed by allopurinol treatment [40]. In both patients, renal function improved.

Although some providers recommend a diet reduced in purines, there are no studies showing that such a diet is helpful. On the other hand, many HPRT-deficient patients have difficulty swallowing and are chronically malnourished, so dietary restrictions may be counterproductive. Until more information regarding the value of a low-purine diet is available, most patients should follow a balanced, high-calorie diet.

Conclusions

LND and its variants are caused by reduced activity of the purine recycling enzyme, HPRT. Although patients with the classic phenotype typically present with a characteristic clinical syndrome that includes overproduction of uric acid and prominent neurobehavioral abnormalities, patients with attenuated phenotypes may be seen where uric acid overproduction may occur without obvious neurological or behavioral features. HPRT deficiency should be suspected in any young individual who presents with evidence of uric acid overproduction, such as unexplained hyperuricemia, uric acid kidney stones, or gout. Allopurinol provides a safe and effective means of treating uric acid overproduction and markedly reduces the risk of nephrolithiasis and gout.

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References

1. Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. *Orphanet. J. Rare Dis.* 2007; 2:48. [PubMed: 18067674]
2. Jinnah, HA.; Friedmann, T. Lesch-Nyhan disease and its variants, in *The Metabolic and Molecular Bases of Inherited Disease*. Scriver, CR., et al., editors. New York: McGraw-Hill; 2001. p. 2537-2570.
3. Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. *Am. J. Med.* 1964; 36:561-570. [PubMed: 14142409]

4. Visser JE, Baer PR, Jinnah HA. Lesch-Nyhan syndrome and the basal ganglia. *Brain Res. Rev.* 2000; 32:449–475. [PubMed: 10760551]
5. Jinnah HA, et al. Delineation of the motor disorder of Lesch-Nyhan disease. *Brain.* 2006; 129:1201–1217. [PubMed: 16549399]
6. Schretlen DS, et al. Neurocognitive functioning in Lesch-Nyhan disease and partial hypoxanthine-guanine phosphoribosyltransferase deficiency. *J. Int. Neuropsychol. Soc.* 2001; 7:805–812. [PubMed: 11771623]
7. Balis ME, et al. Urinary metabolites in congenital hyperuricosuria. *Science.* 1967; 156:1122–1123. [PubMed: 6024192]
8. Sweetman L, Nyhan WL. Excretion of hypoxanthine and xanthine in a genetic disease of purine metabolism. *Nature.* 1967; 215:859–860. [PubMed: 6049739]
9. Kaufman JM, Greene ML, Seegmiller JE. Urine uric acid to creatinine ratio—a screening test for inherited disorders of purine metabolism. *J. Pediatr.* 1968; 73:583–592. [PubMed: 5678000]
10. Jinnah HA, et al. Attenuated variants of Lesch-Nyhan disease. *Brain.* 2010; 133:671–689. [PubMed: 20176575] This is the largest and most comprehensive summary of LND variants published to date, with detailed information on the clinical phenotype and genetics. It questions the value of dividing the phenotype into two or three distinct patient subgroups and instead argues for a continuum of disease severity.
11. Puig JG, et al. The spectrum of hypoxanthine-guanine phosphoribosyltransferase deficiency: clinical experience based on 22 patients from 18 Spanish families. *Medicine.* 2001; 80:102–112. [PubMed: 11307586]
12. Emmerson BT, Thompson L. The spectrum of hypoxanthine-guanine phosphoribosyltransferase deficiency. *Quart. J. Med.* 1973; 166:423–440. [PubMed: 4785440]
13. Kelley WN, et al. Hypoxanthine-guanine phosphoribosyltransferase deficiency in gout. *Ann. Int. Med.* 1969; 70:155–206. [PubMed: 4884382]
14. Catel W, Schmidt J. Uber familiäre gichtische Diathese in Verbindung mit zerebralen und renalen Symptomen bei einem Kleinkind. *Dtsch. Med. Wschr.* 1959; 84:2145–2147. [PubMed: 13808396]
15. Bakay B, et al. Utilization of purines by an HPRT variant in an intelligent, nonmutilative patient with features of the Lesch-Nyhan syndrome. *Pediatr. Res.* 1979; 13:1365–1370. [PubMed: 523196]
16. Bakay B, et al. Variation in human HPRT and its relationship to neurologic and behavioral manifestations. *Adv. Exp. Med. Biol.* 1980; 122A:317–325. [PubMed: 7424650]
17. Marie J, Royer P, Rappaport R. Hyperuricémie congénitale avec troubles neurologiques, renaux et sanguins. *Arch. Fr. Pédiatr.* 1967; 24:501–510. [PubMed: 6059756]
18. Van Bogaert L, Van Damme J, Verschueren M. On a progressive syndrome of extrapyramidal hypertonia with gouty osteoarthropathies in 2 brothers. *Rev. Neurol. (Paris).* 1966; 114:15–32. [PubMed: 5932794]
19. Laplane R, Polonovski C, Graveleau D. Congenital hyperuricemia in a cerebro-renal form. *Arch. Fr. Pédiatr.* 1967; 24:103–104. [PubMed: 6031445]
20. Polonovski C, et al. Encephalopathie et nephropathie métaboliques par hyperuricémie congénitale. *Bull Mem. Soc. Med. Hop. Paris.* 1966; 117:799–812. [PubMed: 5927100]
21. Nyhan WL. Ataxia and disorders of purine metabolism: defects in hypoxanthine guanine phosphoribosyl transferase and clinical ataxia. *Adv. Neurol.* 1978; 21:279–287. [PubMed: 735927]
22. Jinnah HA, et al. The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. *Mutat. Res.* 2000; 463:309–326. [PubMed: 11018746]
23. Jinnah HA, et al. The spectrum of mutations causing HPRT deficiency: an update. *Nucleosides, Nucleotides, Nucl. Acids.* 2004; 23:1153–1160.
24. Becker, MA. Hyperuricemia and gout, in *The metabolic and Molecular Basis of Inherited Disease*. Scriver, CR., et al., editors. New York: McGraw-Hill Book Company; 2001. p. 2513–2535.
25. Murray AW. The biological significance of purine salvage. *Ann. Rev. Biochem.* 1971; 40:811–826. [PubMed: 4330582]
26. Seegmiller JE. Contributions of Lesch-Nyhan syndrome to the understanding of purine metabolism. *J. Inherit. Metab. Dis.* 1989; 12:184–196. [PubMed: 2502677]

27. Rosenbloom FM, et al. Biochemical bases of accelerated purine biosynthesis de novo in human fibroblasts lacking hypoxanthine-guanine phosphoribosyltransferase. *J. Biol. Chem.* 1968; 243:1166–1173. [PubMed: 5650894]
28. Brosh S, et al. De novo synthesis of purine nucleotides in human peripheral blood leukocytes. *J. Clin. Invest.* 1976; 58:289–297. [PubMed: 956368]
29. Sorensen LB. Mechanism of excessive purine biosynthesis in hypoxanthine-guanine phosphoribosyltransferase deficiency. *J Clin Invest.* 1970; 49:968–978. [PubMed: 5441549]
30. So A, Thorens B. Uric acid transport and disease. *J Clin Invest.* 2010; 120:1791–1799. [PubMed: 20516647]
31. Martinon F, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature.* 2006; 440:237–241. [PubMed: 16407889]
32. Ghaemi-Oskouie F, Shi Y. The role of uric acid as an endogenous danger signal in immunity and inflammation. *Curr Rheumatol Rep.* 2011; 13:160–166. [PubMed: 21234729]
33. Torres RJ, Prior C, Puig JG. Efficacy and safety of allopurinol in patients with hypoxanthine-guanine phosphoribosyltransferase deficiency. *Metabolism.* 2007; 56:1179–1186. [PubMed: 17697859]
34. Klinenberg JR, Goldfinger SE, Seegmiller JE. The effectiveness of the xanthine oxidase inhibitor allopurinol in the treatment of gout. *Ann Intern Med.* 1965; 62:639–647. [PubMed: 14274828]
35. Pais VM, et al. Xanthine urolithiasis. *Urol.* 2006; 67:1084.e9–1084.e11. [PubMed: 16698380]
36. Sikora P, et al. Acute renal failure due to bilateral xanthine urolithiasis in a boy with Lesch-Nyhan syndrome. *Pediatr Nephrol.* 2006; 21:1045–1047. [PubMed: 16773422]
37. Oh MM, et al. Urine alkalinization may be enough for the treatment of bilateral renal pelvis stones associated with Lesch-Nyhan syndrome. *Urol Res.* 2011; 39:417–419. [PubMed: 21331772] This article describes a simple and noninvasive method of dissolving uric acid stones in LND.
38. Oka T, et al. Xanthine calculi in the patient with the Lesch-Nyhan syndrome associated with urinary tract infection. *Urol. Int.* 1985; 40:138–140. [PubMed: 3925607]
39. Becker MA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.* 2005; 353:2450–2461. [PubMed: 16339094]
40. Roche A, et al. Efficacy of rasburicase in hyperuricemia secondary to Lesch-Nyhan syndrome. *Am J Kidney Dis.* 2009; 53:677–680. [PubMed: 18992978] This study describes the potential use of a novel therapy for particularly difficult patients with LND who have developed renal failure as a result of nephrolithiasis.

Table 1

Summary of presenting features in previously reported cases of LND

Presenting feature	LND (n=158), % of total ^a	LNV (n=97), % of total
Neurological ^b	82.3	19.6
Urological ^c	9.0	39.2
Gout	1.9	26.8
Other ^d	15.2	11.3

^aThe subgroups may add up to >100% because some cases presented with more than 1 problem

^bNeurological features included items such as developmental delay, various motoric difficulties, and seizures

^cUrological manifestations included items such as renal failure, renal stones without failure, hematuria, and renal colic

^dOther features included family history, unexplained hyperuricemia, and a variety of nonspecific problems such as failure to thrive, feeding difficulties, and unexplained fevers

LND, Lesch-Nyhan disease; LNV, Lesch-Nyhan variant (*Data from* Jinnah et al. [5] and Jinnah et al. [10••].)