Drugs of the Future 2010, 35(5): 421-427

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.5.1490758

LESCH–NYHAN SYNDROME

R.J. Torres[1] and J.G. Puig[2]

[1]Divisions of Clinical Biochemistry and [2]Internal Medicine, Metabolic-vascular Unit, IdiPaz, La Paz University Hospital, Madrid, Spain

CONTENTS

SUMMARY

Lesch–Nyhan syndrome (LNS) is an inborn error of purine metabolism characterized by hyperuricemia, severe action dystonia, choreoathetosis, ballismus, cognitive and attention deficits and self-injurious behavior. The syndrome is associated with complete deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) activity. Partial HGPRT deficiency is termed Lesch–Nyhan variants and includes patients with HGPRT-related gout and a variable degree of neurological involvement but without the complete syndrome. Uric acid overproduction is present in all HGPRT-deficient patients and is associated with lithiasis and gout. Megaloblastic anemia is also associated with the disease. Inheritance of HGPRT deficiency is X-linked recessive, and thus males are generally affected and heterozygous females are carriers (usually asymptomatic). Uric acid overproduction can be managed by allopurinol treatment. Doses must be carefully adjusted to avoid xanthine lithiasis. The importance of new hypouricemic drugs such as uricase and febuxostat needs to be established. The lack of a precise understanding of the neurological dysfunction has precluded the development of useful therapies. Spasticity, when present, and dystonia can be managed with benzodiazepines and γ-aminobutyric acid (GABA) inhibitors such as baclofen. Self-injurious behavior must be managed by a combination of physical restraints, behavioral and pharmaceutical treatments. New agonists and antagonists of adenosine and dopamine receptors may play a role in LNS treatment.

INTRODUCTION

In 1964, M. Lesch and W. Nyhan reported the case of two brothers with a disorder of uric acid metabolism and neurological dysfunction (1). The Lesch–Nyhan syndrome (LNS; OMIM 300322) in a first description included hyperuricemia, mental retardation, self injurious behavior and motor abnormalities such as spasticity and choreoathetosis. In 1967, Seegmiller et al. reported a complete deficiency of the activity of the purine metabolism enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGPRT) as the cause of LNS (2). HGPRT is a key enzyme in the salvage of purine metabolism (Fig. 1). The same year, Kelly et al. described a partial deficiency of HGPRT activity associated with gout and no neurological involvement (3). This partial deficiency was termed Kelly–Seegmiller syndrome or HGPRT-related gout (OMIM 300323). Nowadays it is considered that a continuous spectrum of neurological involvement is present in HGPRT-deficient patients (4, 5). The term Lesch–Nyhan variants has been introduced to include patients with HGPRT-related gout and variable degrees of neurological involvement but without the complete syndrome.

Correspondence: Rosa Torres Jiménez, MD, PhD, Servicio de Bioquímica, Edificio Laboratorio, Hospital Universitario La Paz, Paseo de la Castellana, 261, 28046 Madrid, Spain. E-mail: rtorres.hulp@salud.madrid.org.

CLINICAL DESCRIPTION

Clinical features of HGPRT deficiency include uric acid overproduction-related symptoms, neurological manifestations and hematological disturbances (6).

Hyperuricemia-related renal and articular symptoms (acute arthritis, tophi, nephrolithiasis or urolithiasis and renal disease) are present in all HGPRT-deficient patients and are not related to the severity of the enzyme defect (4). One of the first signs of the disease may be the observation of orange crystals in diapers, crystalluria with obstruction of the urinary tract, or renal failure in the first months of life. A spectrum of neurological manifestations that depend on the severity of the defect may be present in HGPRT-deficient patients. Neurological symptoms affect the motor sphere, cognitive and behavioral aspects (5).

In the complete syndrome, patients are normal at birth. Psychomotor delay becomes evident within 3-6 months, with delayed acquisition of sitting and head support with hypotonia. Self-mutilation, manifested as lip biting or finger chewing, can appear as soon as teeth are present. The motor syndrome evolves to a severe action dystonia, superimposed on a baseline hypotonia. Its severity leads to an inability to stand up and walk, with patients being confined to a wheelchair. Involuntary movements such as choreoathetosis and ballismus are usually associated with voluntary movements and increase with excitement and anxiety. Dysarthria and dysphagia are always present and opisthotonus is frequently reported. Corticospinal tract signs such as spasticity, hyperreflexia and exten-

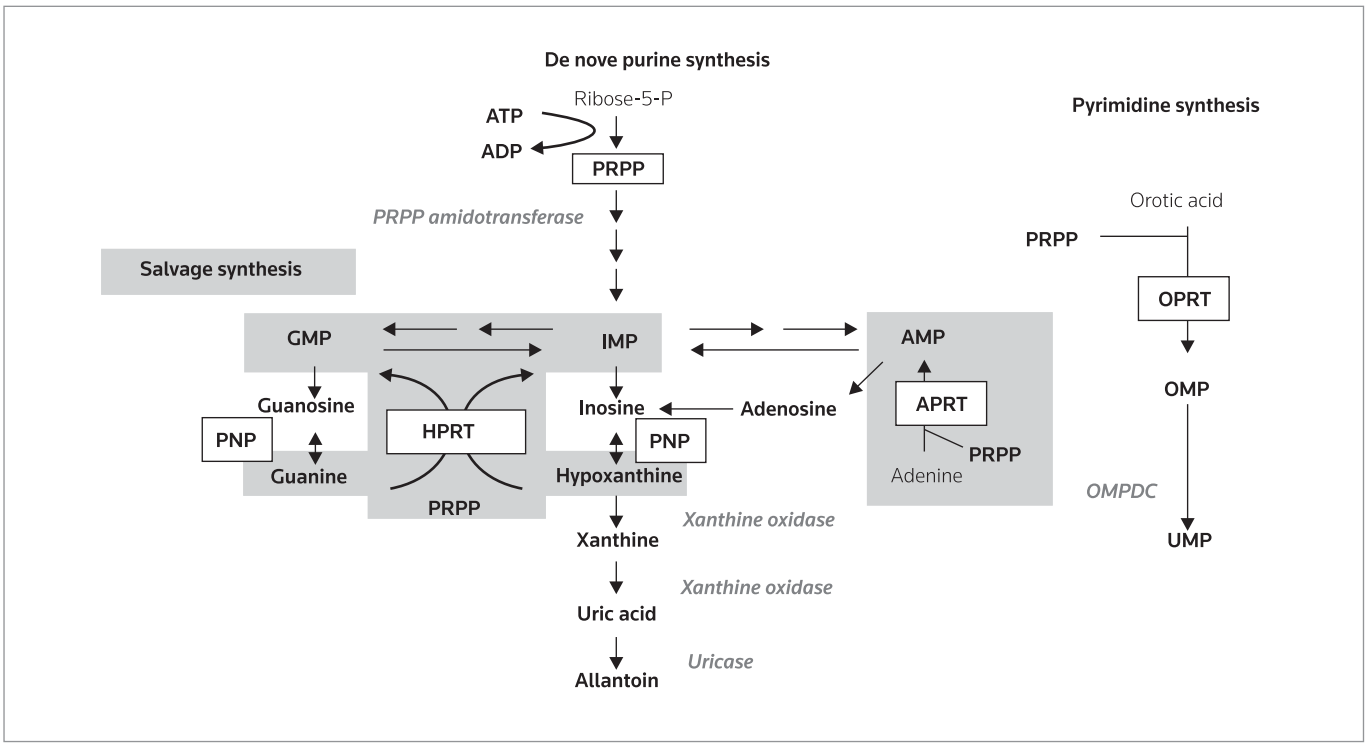

Figure 1. Purine metabolism. The metabolic scheme shows the first and rate-limiting step of de novo purine synthesis mediated by the enzyme phosphoribosyl pyrophosphate (PRPP) amidotransferase, and the salvage pathway mediated by hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and adenine phosphoribosyltransferase (APRT). The de novo synthesis occurs through a multistep process and requires the contribution of four amino acids, one PRPP, two folates and three ATP to synthesize an inosine monophosphate (IMP) molecule. HGPRT catalyzes the salvage synthesis of IMP and guanosine monophosphate (GMP) from the purine bases hypoxanthine and guanine, respectively, utilizing PRPP as a cosubstrate. The HGPRT defect results in the accumulation of the substrates hypoxanthine and guanine, which are converted to uric acid by means of xanthine oxidase. Elevated APRT activity may also contribute to purine overproduction. 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. Allopurinol is a substrate of purine and pyrimidine metabolic enzymes, such as HGPRT or orotate phosphoribosyltransferase (OPRT). Allopurinol causes inhibition of purine nucleoside phosphorylase (PNP) and orotidine-5'-monophosphate decarboxylase (OMPDC).

sor plantar reflex are generally reported in later years and they may reflect an acquired defect (7). The first description of LNS included mental retardation as a characteristic of the syndrome. However, completely HGPRT-deficient patients, when evaluated with specific tests for motor difficulties, show mild to moderate mental retardation (8-10).

Compulsive self-injurious behavior, the most striking feature of LNS, is only present in patients with complete enzyme defect. The patients bite their lips, tongue or fingers, causing important automutilating lesions. In some instances, the aggressive behavior is also directed towards family and friends, with patients spitting or using abusive language. The mutilation is not due to a lack of sensation (the patients feel pain and are relieved when protected from self), and recently it has been ascribed to an obsessive–compulsive behavior. Self-mutilation may start between 2 and 16 years of age and evolves with periods of different intensity (11, 12). Generally, it is associated with or aggravated by psychological stress (adolescence, family conflicts) or concomitant diseases. Despite their periodic aggressive behavior, LNS patients are frequently happy and engaging children when they are restrained. The neurobehavioral disorder may be markedly modulated by numerous environmental factors, among which education is the most relevant. LNS patients present megaloblastic anemia (13). Microcytic anemia is also frequent and in some cases associated with hiatus hernia (4, 6).

In LNS variants a complete motor syndrome may be present in the most severe forms, but self-injurious behavior is always absent (5). In these cases, generalized dystonia precludes standing up and walking, and involuntary movements are present. In other variant patients the grade of dystonia is less severe and appears in the form of a dystonic gait, speech difficulties and exercise-induced dystonia, or is unapparent (4). These patients can lead independent lives. They can present variable degrees of mental retardation or show normal intelligence, although usually displaying attention deficits.

The prevalence of the disease is estimated to be 1/380,000 live births in Canada and 1/235,000 live births in Spain (6, 14).

GENETICS

Human HGPRT is encoded by a gene located on the long arm of the X chromosome and HGPRT deficiency is inherited as a recessive X-linked trait (15). Thus, males are generally affected and women are

generally asymptomatic carriers. At least five women with LNS due to a variety of molecular mechanisms have been described in the literature (16-20). *HPRT* mutations accounting for HGPRT deficiency are heterogeneous in type and localization (21-23). More than 300 disease-associated mutations (deletions, insertions, duplications and point mutations) are found dispersed within the gene (24).

DIAGNOSIS

The diagnosis of HGPRT deficiency must be supported by clinical, biochemical, enzymatic and molecular data. Hyperuricemia with hyperuricosuria is the biochemical hallmark that prompts an enzymatic diagnosis (25). Patients present low or undetectable HGPRT activity in hemolysates, with increased adenine phosphoribosyltransferase (APRT) activity. To better characterize the HGPRT deficiency, in order to find a possible residual activity, enzyme activity can be measured in intact cells (erythrocytes or fibroblasts) (4, 26).

The molecular diagnosis of HGPRT deficiency requires analysis of the HGPRT coding region by RT-PCR, or genomic analysis of the *HPRT* gene of each patient in order to find the patients' particular mutation (27, 28). In some cases, the HGPRT coding region is normal and the patients present decreased HGPRT mRNA expression of unknown origin (29, 30). About 30% of the patients carry de novo mutations but about 70% of the mothers are somatic carriers. Molecular diagnosis in HGPRT-deficient patients allows faster and more accurate carrier and prenatal diagnosis (31).

ETIOLOGY

Uric acid overproduction

HGPRT catalyzes the salvage synthesis of inosine monophosphate (IMP) and guanosine monophosphate (GMP) from the purine bases hypoxanthine and guanine, respectively, utilizing phosphoribosyl pyrophosphate (PRPP) as a cosubstrate (Fig. 1). HGPRT deficiency results in the accumulation of its substrates hypoxanthine and guanine and PRPP. Hypoxanthine is converted to uric acid by means of xanthine oxidase and the increased availability of PRPP for PRPP amidotransferase increases de novo purine synthesis. On the other hand, there is a decrease IMP and GMP, which are PRPP amidotransferase feedback inhibitors. This dual mechanism results in an increased de novo synthesis of purine nucleotides (32).

Pathophysiology of neurological symptoms

The connection between the aberrant purine metabolism and the neurological and behavioral characteristics remains unknown. Imaging studies and post mortem examination of brains from LNS patients have not disclosed any characteristic morphological abnormality; thus, a functional instead of a morphological alteration is postulated (33, 34). Clinical data suggest a basal ganglia alteration. Both extrapyramidal motor syndrome, with involuntary movements and dystonia, and behavioral disturbances are signs of basal ganglia damage (35).

Several neurotransmitter changes seem to be implicated in the pathophysiology of LNS. Neurochemical analysis of post mortem tissues and cerebrospinal fluid analysis showed decreased levels of dopamine and the dopamine metabolite homovanillic acid, whereas serotonin and 5-hydroxyindolacetic levels show discrepant results (36-38). Studies with positron emission tomography and ligands that bind to dopamine-related proteins confirmed an alteration of the dopaminergic system in LNS patients (39, 40). Dopamine deficiency in the striatum has been confirmed in animal models of HGPRT deficiency (41, 42).

Alterations in other neurotransmitter systems, such as adenosine, have also been implicated in patients with LNS (43). In addition to their well-known intracellular functions related to DNA and RNA synthesis, purine nucleotides are released into the extracellular space, where they act as intercellular signaling molecules (44). Adenosine has been related to motor and behavioral changes through its actions on specific receptors on the neuron cell surface. Self-injurious behavior in rats has been related to adenosine action on the A_{2A} receptor subtype, which is abundant in basal ganglia (45-47). Moreover, an A_{2A} receptor agonist has been shown to exert antidystonic effects in a dystonic animal model (48). Adenosine transport and function have been found to be abnormal in HGPRT-deficient cells (43, 49). Moreover, adenosine and dopamine receptors are coupled and adenosine agonists and antagonists modulate dopaminergic neurotransmission, which appears to be altered in LNS (50). As a consequence of HGPRT deficiency, LNS patients' cerebrospinal fluid showed increased hypoxanthine concentrations (51). Toxic effects of this metabolite have been implicated in the pathogenesis of neurological dysfunction by means of an alteration in adenosine transport, Na^+/K^+-ATPase activity, serotonin content and neuronal development (52-59). Deficit of other purine compounds due to the enzyme defect is controversial and altered nucleotide concentrations have been postulated as a possible cause of changes in G-protein-mediated signal transduction (60). Finally, a defective developmental process of dopaminergic neurons is thought to be implicated in the neurological manifestations of LNS (61).

Hematological aspects

Megaloblastic anemia in LNS patients is associated with megaloblastic findings in bone marrow. Ineffective erythropoiesis has been postulated as the cause of anemia in LNS patients and increased folic acid consumption due to enhanced de novo purine synthesis has also been implicated in the pathogenesis of anemia (63). Nevertheless, this anemia is not corrected by folate therapy.

TREATMENT

Uric acid overproduction

Uric acid overproduction is effectively controlled with the xanthine oxidase inhibitor allopurinol, which blocks the conversion of xanthine and hypoxanthine to uric acid. Allopurinol is a purine analogue that is metabolized to the active enzyme inhibitor oxypurinol by xanthine oxidase. Oxypurinol is excreted by the kidney and oxypurinol concentrations are frequently elevated in patients with renal impairment (64). Allopurinol has no effect on behavioral and neurological symptoms, but it should be started as soon as the enzyme deficiency has been diagnosed in order to avoid renal damage. In adults, or when there are great tissue urate deposits, combined treatment with colchicine prophylaxis is required to avoid gout flares. The

optimal allopurinol dose for HGPRT-deficient patients has not been established, but, in our experience, when serum urate is maintained close to its solubility threshold, urate deposition does not occur and xanthine lithiasis may be avoided. Recommended doses of allopurinol in LNS patients range from 50 to 600 mg/day. The initial dosage of allopurinol is 5-10 mg/kg/day and it should be adjusted to maintain high–normal serum uric acid levels and a (urinary) uric acid/creatinine ratio of < 1.0. In our experience, treatment with allopurinol normalized serum urate levels in all HGPRT-deficient patients and resulted in a mean reduction of serum urate of about 50% and a 74% reduction in the (urinary) uric acid/creatinine ratio. Allopurinol inhibition of xanthine oxidase accounted for increased hypoxanthine and xanthine urinary excretion rates ranging from 5- to 10-fold when compared to baseline levels in these patients (65).

Under normal conditions, allopurinol increases the reutilization of hypoxanthine for nucleotide and nucleic acid synthesis via HGPRT activity. The resulting increase in nucleotide concentration leads to feedback inhibition of de novo purine synthesis. However, in HGPRT-deficient patients, hypoxanthine cannot be reutilized and there is increased purine production, as occurs in malignancies and their treatment. Under these circumstances, the absolute concentration of xanthine could rise to a level at which deposition in the urinary tract may occur and xanthine lithiasis may develop as a consequence of allopurinol therapy. In our experience, xanthine lithiasis may be prevented by sequential determination of urinary oxypurines, which should be at a certain balance with uric acid excretion and by titrating allopurinol doses to maintain high–normal serum uric acid levels.

Allopurinol should be accompanied by adequate hydration to achieve maximum diuresis. Alkalinization, of considerable benefit in relation to urate stones, may be less so in relation to xanthine stones. Allopurinol treatment reduces serum urate and urine uric acid levels, preventing uric acid crystalluria, nephrolithiasis, gouty arthritis and tophi in LNS patients. With adequate allopurinol doses and compliance, renal function usually remains stable or even improves with therapy.

Allopurinol hypersensitivity has been described in 0.4% of patients receiving this treatment. The higher incidence of hypersensitivity in patients with decreased renal function has prompted the adjustment of allopurinol doses according to creatinine clearance. However, this procedure does not always prevent allopurinol hypersensitivity (66). To our knowledge, no hypersensitivity reaction has been described in LNS patients despite impaired renal function.

In most mammals, the hepatic enzyme uricase, or urate oxidase, transforms uric acid to a more soluble compound, allantoin (Fig. 1). In humans, due to a mutation in the uricase gene, uric acid is the last product of purine metabolism. Rasburicase, a uricase purified from *Aspergillus flavus*, is employed to prevent tumor lysis syndrome in hematological malignancies, administered i.v. at doses of 0.20 mg/kg/day during a short period of 5-7 days. In HGPRT-deficient patients, xanthine lithiasis could be avoided by uricase treatment. However, there is no long-term evidence of the safety of rasburicase treatment and it is known to be antigenic. Its short half-life (18 h) and its form of administration (injection) do not appear to be very convenient for chronic therapy (67). However, rasburicase appears to be effective in infants with acute kidney injury (68). In our experience, two LNS patients who presented with renal failure in the first months of life were treated with rasburicase during a short period of time at established doses, followed by allopurinol treatment. In both patients, renal function improved with rasburicase treatment (69).

A genetically engineered, recombinant, polyethylene glycol (PEG)-conjugated mammalian uricase (pegloticase) has been developed with the potential to reduce immunogenicity and have a longer half-life. This uricase could be administered i.v. every 2-4 weeks to maintain serum urate levels within normal limits. Results of phase I studies showed that anti-pegloticase antibodies were present in 75% of treated patients and these antibodies were associated with a reduced circulating half-life of pegloticase in some patients. Infusion reactions were also frequent (70).

Febuxostat is a novel nonpurine inhibitor recently marketed for the treatment of hyperuricemia and gout (71). Febuxostat is a potent inhibitor of both the oxidized and reduced forms of the enzyme xanthine oxidase. However, allopurinol and oxypurinol inhibit only one form of the enzyme. This difference has been postulated to account for the greater potency and long-lasting effect of febuxostat. On the other hand, in contrast to allopurinol, febuxostat is not a substrate for purine and pyrimidine metabolic enzymes such as HGPRT or orotate phosphoribosyltransferase, and it does not inhibit the enzymatic activity of purine nucleoside phosphorylase and orotidine-5′-monophosphate decarboxylase (Fig. 1) (72). To our knowledge, febuxostat treatment has not been employed in HGPRT-deficient patients, but it could be an alternative to allopurinol.

Motor syndrome

As in many generalized dystonic syndromes, the lack of a precise understanding of the cause of neurological dysfunction has precluded the development of useful therapies in HGPRT deficiency. Rigorous placebo-controlled studies have not been conducted in LNS patients. Spasticity and dystonia can be managed with benzodiazepines and GABA inhibitors such as baclofen (6). No medication has been found to effectively control the extrapyramidal manifestations of the disease.

Dopamine replacement therapy in LNS patients has been reported in a few noncontrolled studies with very heterogeneous responses (73). Most of the treated patients presented intolerable side effects. This could be due to the coexistence in HGPRT deficiency of dopamine hypersensitivity and high dopamine receptor expression, in addition to the dopamine content deficit (74, 75). Both adenosine and dopamine receptor expression is altered in HGPRT-deficient cells (74). These facts emphasize a pivotal role for disrupted adenosine and dopamine neurotransmission in the pathogenesis of neurological manifestations of LNS. The safety and efficacy of istradefylline, a selective adenosine A_{2A} receptor antagonist, have been evaluated in levodopa-treated Parkinson's disease subjects with motor complications. In the future, adenosine receptor modulation could be a potential target for LNS (76).

Today, physical rehabilitation, including the management of dysarthria and dysphagia, special devices to enable hand control of objects, appropriate walking aids, and a program of posture man-

agement to prevent deformities is the key to the management of the motor manifestations of LNS.

Behavioral manifestations

Self-injurious behavior must be managed with a combination of physical restraints, behavioral and pharmaceutical treatments. Benzodiazepines and carbamazapine are sometimes useful for ameliorating behavioral manifestations and anxiety (6, 11). Stress increases self-injurious behavior. Thus, stressful situations should be avoided and adverse techniques should not be employed. Instead, behavioral extinction methods have proven to be partially effective in a controlled setting. Some reports have suggested that the antiepileptic drug gabapentin may improve self-injurious behavior and no side effects have been associated with its use (77). However, no controlled trials have been conducted in LNS patients. The atypical antipsychotic drug risperidone, a nonselective antagonist of both 5-HT_{2A} and dopamine D_2 receptors, has been found to reduce self-injurious behavior in some LNS patients (78). Recently, the selective dopamine D_1/D_5 receptor antagonist ecopipam received orphan designation from the European Commission for the treatment of LNS and a pilot trial is being conducted in the U.S.

Other treatments under investigation for the management of self-injurious behavior include local injections of botulinum toxin (79-81). Several authors have reported the use of repeated botulinum toxin A injections into the bilateral masseters or into the facial muscles to prevent tongue and lip biting in LNS patients. In our patients, botulinum toxin injection is usually effective for a limited period of time. When injecting, the masseters toxin could spread to pharyngeal muscles, causing dysphagia. As self-injurious intensity varies, this procedure could be useful in the most aggressive periods to avoid tissue damage.

Deep brain stimulation in the globus pallidus has been reported to improve self-injurious behavior in a few LNS patients, but the efficacy and safety of this therapy need to be demonstrated in the long-term management of these patients (82, 83).

Nowadays, the cornerstone of day-to-day management of LNS self-injurious behavior is still adapted physical restraint to protect patients from themselves (6). For instance, elbow restraints allow hand use without the possibility of finger mutilation and dental guards prevent cheek biting. Patients themselves request restrictions and become anxious if they are unrestrained, and sometimes restraints that would appear to be ineffective, such as a pair of gloves to prevent finger biting, are very useful.

ACKNOWLEDGMENTS

This work was supported by Grants FIS 08/0009, and by CIBERER (Centro de Investigación Biomédica en Red para el estudio de las enfermedades raras).

DISCLOSURES

The authors state no conflicts of interest.

REFERENCES

1. Lesch, M., Nyhan, W.L. *A familial disorder of uric acid metabolism and central nervous system function*. Am J Med 1964, 36: 561-70.
2. Seegmiller, J.E., Rosenbloom, F.M., Kelley, W.N. *Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis*. Science 1967, 155 (3770): 1682-4.
3. Kelley, W.N., Rosenbloom, F.M., Henderson, J.F., Seegmiller, J.E. *A specific enzyme defect in gout associated with overproduction of uric acid*. Proc Natl Acad Sci U S A 1967, 57(6): 1735-9.
4. García Puig, J., Torres Jiménez, R., Mateos, F., Ramos, T., Arcas, J., Buño, A., O'Neill, P. *The spectrum of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. Clinical experience based on 22 patients from 18 Spanish families.* Medicine (Balt) 2001, 80(2): 102-12.
5. Jinnah, H.A., Ceballos-Picot, I., Torres, R.J. et al. *Attenuated variants of Lesch-Nyhan disease.* Brain 2010, 133(3): 671-89.
6. Torres, R.J., Puig, J.G. *Hypoxanthine-guanine phosophoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome*. Orphanet J Rare Dis 2007, 2: 48.
7. Jinnah, H.A., Visser, J.E., Harris, J.C. et al. *Delineation of the motor disorder of Lesch-Nyhan disease*. Brain 2006, 129(5): 1201-17.
8. Schretlen, D.J., Harris, J.C., Park, K.S., Jinnah, H.A., del Pozo, N.O. *Neurocognitive functioning in Lesch-Nyhan disease and partial hypoxanthine-guanine phosphoribosyltransferase deficiency*. J Int Neuropsychol Soc 2001, 7(7): 805-12.
9. Matthews, W.S., Solan, A., Barabas, G., Robey, K. *Cognitive functioning in Lesch-Nyhan syndrome: A 4-year follow-up study*. Dev Med Child Neurol 1999, 41(4): 260-2.
10. Anderson, L.T., Ernst, M., Davis, S.V. *Cognitive abilities of patients with Lesch-Nyhan disease*. J Autism Dev Disord 1992, 22(2): 189-203.
11. Anderson, L.T., Ernst, M. *Self-injury in Lesch-Nyhan disease*. J Autism Dev Disord 1994, 24(1): 67-81.
12. Schroeder, S.R., Oster-Granite, M.L., Berkson, G. et al. *Self-injurious behavior: Gene-brain-behavior relationships*. Ment Retard Dev Disabil Res Rev 2001, 7(1): 3-12.
13. van der Zee, S.P., Schretlen, E.D., Monnens, L.A. *Megaloblastic anaemia in the Lesch-Nyhan syndrome*. Lancet. 1968, 1(7557): 1427.
14. Crawhall, J.C., Henderson, J.F., Kelley, W.N. *Diagnosis and treatment of the Lesch-Nyhan syndrome.* Pediatr Res 1972, 6(5): 504-13.
15. Edwards, A., Voss, H., Rice, P. et al. *Automated DNA sequencing of the human HPRT locus.* Genomics 1990, 6(4): 593-608.
16. Ogasawara, N., Stout, J.T., Goto, H., Sonta, S.I., Matsumoto, A., Caskey, C.T. *Molecular analysis of a female Lesch-Nyhan patient*. J Clin Invest 1989, 84(3): 1024-7.
17. Rinat, C., Zoref-Shani, E., Ben-Neriah, Z. et al. *Molecular, biochemical, and genetic characterization of a female patient with Lesch-Nyhan disease.* Mol Genet Metab 2006, 87(3): 249-52.
18. De Gregorio, L., Jinnah, H.A., Harris, J.C. et al. *Lesch-Nyhan disease in a female with a clinically normal monozygotic twin*. Mol Genet Metab 2005, 85(1): 70-7.
19. De Gregorio, L., Nyhan, W.L., Serafin, E., Chamoles, N.A. *An unexpected affected female patient in a classical Lesch-Nyhan family.* Mol Genet Metab. 2000, 69(3): 263-8.
20. Aral, B., de Saint Basile, G., Al-Garawi, S., Kamoun, P., Ceballos-Picot, I. *Novel nonsense mutation in the hypoxanthine guanine phosphoribosyltransferase gene and nonrandom X-inactivation causing Lesch-Nyhan syndrome in a female patient.* Hum Mutat 1996, 7(1): 52-8.

21. Wilson, J.M., Stout, J.T., Palella, T.D., Davidson, B.L., Kelley, W.N., Caskey, C.T. *A molecular survey of hypoxanthine-guanine phosphoribosyltransferase deficiency in man*. J Clin Invest 1986, 77(1): 188-95.
22. Jinnah, H.A., De Gregorio, L., Harris, J.C., Nyhan, W.L., O'Neill, J.P. *The spectrum of inherited mutations causing HPRT deficiency: 75 New cases and a review of 196 previously reported cases.* Mutat Res 2000, 463(3): 309-26.
23. Torres, R.J., Mateos, F.A., Molano, J. et al. *Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in thirteen Spanish families.* Hum Mutat 2000, 15(4): 383.
24. Official website of the Lesch-Nyhan disease Study Group. www.lesch-nyhan.org.
25. Kaufman, J.M., Greene, M.L., Seegmiller, J.E. *Urine uric acid to creatinine ratio—a screening test for inherited disorders of purine metabolism. Phosphoribosyltransferase (PRT) deficiency in X-linked cerebral palsy and in a variant of gout*. J Pediatr 1968, 73(4): 583-92.
26. Page, T., Bakay, B., Nissinen, E., Nyhan, W.L. *Hypoxanthine-guanine phosphoribosyltransferase variants: Correlation of clinical phenotype with enzyme activity.* J Inherit Metab Dis 1981, 4(4): 203-6.
27. Davidson, B.L., Tarle, S.A., Palella, T.D., Kelley, W.N. *Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in ten subjects determined by direct sequencing of amplified transcripts.* J Clin Invest 1989, 84(1): 342-6.
28. Gibbs, R.A., Nguyen, P.N., Edwards, A., Civitello, A.B., Caskey, C.T. *Multiplex DNA deletion detection and exon sequencing of the hypoxanthine phosphoribosyltransferase gene in Lesch-Nyhan families*. Genomics 1990, 7(2): 235-44.
29. Dawson, P.A., Gordon, R.B., Keough, D.T., Emmerson, B.T. *Normal HPRT coding region in a male with gout due to HPRT deficiency*. Mol Genet Metab 2005, 85(1): 78-80.
30. García, M.G., Torres, R.J., Prior, C., Puig, J.G. *Normal HPRT coding region in complete and partial HPRT deficiency.* Mol Genet Metab 2008, 94(2): 167-72.
31. O'Neill, J.P. *Mutation carrier testing in Lesch-Nyhan syndrome families: HPRT mutant frequency and mutation analysis with peripheral blood T lymphocytes*. Genet Test 2004, 8(1): 51-64.
32. Rosenbloom, F.M., Henderson, J.F., Caldwell, I.C., Kelley, W.N., Seegmiller, J.E. *Biochemical bases of accelerated purine biosynthesis de novo in human fibroblasts lacking hypoxanthine-guanine phosphoribosyltransferase*. J Biol Chem 1968, 243(6): 1166-73.
33. Watts, R.W., Spellacy, E., Gibbs, D.A., Allsop, J., McKeran, R.O., Slavin, G.E. *Clinical, post-mortem, biochemical and therapeutic observations on the Lesch-Nyhan syndrome with particular reference to the neurological manifestations*. Q J Med 1982, 51(201): 43-78.
34. Harris, J.C., Lee, R.R., Jinnah, H.A., Wong, D.F., Yaster, M., Bryan, R.N. *Craniocerebral magnetic resonance imaging measurement and findings in Lesch-Nyhan syndrome*. Arch Neurol 1998, 55(4): 547-53.
35. Visser, J.E., Bar, P.R., Jinnah, H.A. *Lesch-Nyhan disease and the basal ganglia.* Brain Res Rev 2000, 32(2-3): 449-75.
36. Lloyd, K.G., Hornykiewicz, O., Davidson, L. et al. *Biochemical evidence of dysfunction of brain neurotransmitters in the Lesch-Nyhan syndrome*. N Engl J Med 1981, 305(9): 1106-11.
37. Silverstein, F.S., Johnston, M.V., Hutchinson, R.J., Edwards, N.L. *Lesch-Nyhan syndrome: CSF neurotransmitter abnormalities*. Neurology 1985, 35(6): 907-11.
38. Jankovic, J., Caskey, C.T., Stout, J.T., Butler, I.J. *Lesch Nyhan syndrome: a study of motor behavior and cerebrospinal fluid neurotransmitters.* Ann Neurol 1988, 23(5): 466-9.
39. Ernst, M., Zametkin, A.J., Matochik, J.A. et al. *Presynaptic dopaminergic deficits in Lesch-Nyhan disease.* N Engl J Med 1996, 334(24): 1568-72.
40. Wong, D.F., Harris, J.C., Naidu, S. et al. *Dopamine transporters are markedly reduced in Lesch-Nyhan disease in vivo.* Proc Natl Acad Sci U S A 1996, 93(11): 5539-43.
41. Breese, G.R., Criswell, H.E., Duncan, G.E., Mueller, R.A. *A dopamine deficiency model of Lesch-Nyhan disease—The neonatal-6-OHDA-lesioned rat.* Brain Res Bull 1990, 25(3): 477-84.
42. Jinnah, H.A., Wojcik, B.E., Hunt, M. et al. *Dopamine deficiency in a genetic mouse model of Lesch-Nyhan disease.* J Neurosci 1994, 14(3, Pt. 1): 1164-75.
43. Torres, R.J., Deantonio, I., Prior, C., Puig, J.G. *Adenosine transport in peripheral blood lymphocytes from Lesch-Nyhan patients*. Biochem J 2004, 377(Pt. 3): 733-9.
44. Dunwiddie, T.V., Masino, S.A. *The role and regulation of adenosine in the central nervous system*. Annu Rev Neurosci 2001, 24(4): 31-55.
45. Ushijima, I., Katasuragi, T., Furukawa, T. *Involvement of adenosine receptor activities in aggressive responses produced by clonidine in mice*. Psychopharmacology 1984, 83(4): 335-9.
46. Lloyd, H.G., Stone, T.W. *Chronic methylxanthine treatment in rats: A comparison of Wistar and Fisher 344 strains.* Pharmacol Biochem Behav 1981, 14(6): 827-30.
47. Ledent, C., Vaugeois, J.M., Schiffmann, S.N. et al. *Aggressiveness, hypoalgesia and high blood pressure in mice lacking the adenosine A2a receptor*. Nature (London) 1997, 388(6643): 674-8.
48. Richter, A., Hamann, M., Bartling, C. *CGS-21680 exerts marked antidystonic effects in a genetic model of paroxysmal dyskinesia*. Eur J Pharmacol 2000, 404: 299-302.
49. Prior, C., Torres, R.J., Puig, J.G. *Hypoxanthine decreases equilibrative type of adenosine transport in lymphocytes from Lesch-Nyhan patients*. Eur J Clin Invest 2007, 37(11): 905-11.
50. Ferré, S., Quiroz, C., Woods, A.S. et al. *An update on adenosine A2A-dopamine D2 receptor interactions: Implications for the function of G protein-coupled receptors*. Curr Pharm Des 2008, 14(15): 1468-74.
51. Harkness, R.A., McCreanor, G.M., Watts, R.W. *Lesch-Nyhan syndrome and its pathogenesis: Purine concentrations in plasma and urine with metabolite profiles in CSF.* J Inherit Metab Dis 1988, 11(3): 239-52.
52. Prior, C., Torres, R.J., Puig, J.G. *Hypoxanthine effect on equilibrative and concentrative adenosine transport in human lymphocytes: implications in the phatogenesis of Lesch-Nyhan syndrome.* Nucleosides Nucleotides Nucleic Acids 2006, 25(9-11): 1065-9.
53. Bavaresco, C.S., Chiarani, F., Wannmacher, C.M., Netto, C.A., Wyse, A.T. *Intrastriatal hypoxanthine reduces Na(+),K (+)-ATPase activity and induces oxidative stress in the rats*. Metab Brain Dis 2007, 22(1): 1-11.
54. Bavaresco, C.S., Chiarani, F., Duringon, E. et al. *Intrastriatal injection of hypoxanthine reduces striatal serotonin content and impairs spatial memory performance in rats*. Metab Brain Dis 2007; 22(1): 67-76.
55. Bavaresco, C.S., Chiarani, F., Kolling, J. et al. *Intrastriatal injection of hypoxanthine alters striatal ectonucleotidase activities: A time-dependent effect*. Brain Res 2008, 1239: 198-206.
56. Bavaresco, C.S., Ben, J., Chiarani, F., Netto, C.A., Wyse, A.T. *Intrastriatal injection of hypoxanthine impairs memory formation of step-down inhibitory avoidance task in rats*. Pharmacol Biochem Behav 2008, 90(4): 594-7.
57. Bavaresco, C.S., Chiarani, F., Kolling, J., Netto, C.A., de Souza Wyse, A.T. *Biochemical effects of pretreatment with vitamins E and C in rats submitted to intrastriatal hypoxanthine administration.* Neurochem Int 2008, 52(6): 1276-83.

58. Bavaresco, C.S., Chiarani, F., Wajner, M., Netto, C.A., de Souza Wyse, A.T. *Intrastriatal hypoxanthine administration affects Na+,K+-ATPase, acetylcholinesterase and catalase activities in striatum, hippocampus and cerebral cortex of rats*. Int J Dev Neurosci 2006, 24(7): 411-7.

59. Ma, M.H., Stacey, N.C., Connolly, G.P. *Hypoxanthine impairs morphogenesis and enhances proliferation of a neuroblastoma model of Lesch Nyhan syndrome*. J Neurosci Res 2001, 63(6): 500-8.

60. Messina, E., Micheli, V., Giacomello, A. *Guanine nucleotide depletion induces differentiation and aberrant neurite outgrowth in human dopaminergic neuroblastoma lines: A model for basal ganglia dysfunction in Lesch-Nyhan disease*. Neurosci Lett 2005, 375(2): 97-100.

61. Guibinga, G.H., Hsu, S., Friedmann, T. *Deficiency of the housekeeping gene hypoxanthine-guanine phosphoribosyltransferase (HPRT) dysregulates neurogenesis*. Mol Ther 2010, 18(1): 54-62.

62. Ceballos-Picot, I., Mockel, L., Potier, M.C. et al. *Hypoxanthine-guanine phosphoribosyl transferase regulates early developmental programming of dopamine neurons: implications for Lesch-Nyhan disease pathogenesis*. Hum Mol Genet 2009, 18(13): 2317-27.

63. Samson, D., Halliday, D., Nicholson, D.C., Chanarin, I. *Quantitation of ineffective erythropoiesis from the incorporation of [15N] delta-aminolaevulinic acid and [15N] glycin into early labelled bilirubin. II. Anaemic patients*. Br J Haematol 1976, 34(1): 45-53.

64. Rundles, R.W. *The development of allopurinol*. Arch Intern Med 1985, 145(8): 1492-503.

65. Torres, R.J., Prior, C., Puig, J.G. *Efficacy and safety of allopurinol in patients with hypoxanthine-guanine phosphoribosyltransferase deficiency*. Metabolism 2007, 56(9): 1179-86.

66. Chao, J., Terkeltaub, R. *A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout*. Curr Rheumatol Rep 2009, 11(2): 135-40.

67. Ali, S., Lally, E.V. *Treatment failure gout.* Med Health R I 2009, 92(11): 369-71.

68. Hobbs, D.J., Steinke, J.M., Chung, J.Y., Barletta, G.M., Bunchman, T.E. *Rasburicase improves hyperuricemia in infants with acute kidney injury.* Pediatr Nephrol 2010, 25(2): 305-9.

69. Roche, A., Pérez-Dueñas, B., Camacho, J.A. et al. *Efficacy of rasburicase in hyperuricemia secondary to Lesch-Nyhan syndrome.* Am J Kidney Dis 2009, 53(4): 677-80.

70. Sundy, J.S., Becker, M.A., Baraf, H.S. et al. *Pegloticase Phase 2 Study Investigators. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: Results of a phase II randomized study.* Arthritis Rheum 2008, 58(9): 2882-91.

71. Becker, M.A., Schumacher, H.R., Espinoza, L.R. et al. *The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial.* Arthritis Res Ther 2010, 12(2): R63.

72. Takano, Y., Hase-Aoki, K., Horiuchi, H. et al. *Selectivity of febuxostat, a novel non-purine inhibitor of xanthine oxidase/xanthine dehydrogenase*. Life Sci 2005, 76(16): 1835-47.

73. Serrano, M., Pérez-Dueñas, B., Ormazábal, A. et al. *Levodopa therapy in a Lesch-Nyhan disease patient: pathological, biochemical, neuroimaging, and therapeutic remarks*. Mov Disord 2008, 23(9): 1297-300.

74. García, M.G., Puig, J.G., Torres, R.J. *Abnormal adenosine and dopamine receptor expression in lymphocytes of Lesch-Nyhan patients*. Brain Behav Immun 2009, 23(8): 1125-31.

75. Saito, Y., Ito, M., Hanaoka, S., Ohama, E., Akaboshi, S., Takashima, S. *Dopamine receptor upregulation in Lesch-Nyhan syndrome: A postmortem study.* Neuropediatrics 1999, 30(2): 66-71.

76. Stone, T.W., Ceruti, S., Abbracchio, M.P. *Adenosine receptors and neurological disease: neuroprotection and neurodegeneration*. Handb Exp Pharmacol 2009, (193): 535-87.

77. McManaman, J., Tam, D.A. *Gabapentin for self-injurious behavior in Lesch-Nyhan syndrome.* Pediatr Neurol 1999, 20(5): 381-2.

78. Allen, S.M., Rice, S.N. *Risperidone antagonism of self-mutilation in a Lesch-Nyhan patient*. Prog Neuropsychopharmacol Biol Psychiatry 1996, 20(5): 793-800.

79. Gutierrez, C., Pellene, A., Micheli, F. *Botulinum toxin: Treatment of self-mutilation in patients with Lesch-Nyhan syndrome*. Clin Neuropharmacol 2008, 31(3): 180-3

80. Schneider, S.A., Aggarwal, A., Bhatt, M. et al. *Severe tongue protrusion dystonia: clinical syndromes and possible treatment.* Neurology 2006, 67(6): 940-3.

81. Dabrowski, E., Smathers, S.A., Ralstrom, C.S., Nigro, M.A., Leleszi, J.P. *Botulinum toxin as a novel treatment for self-mutilation in Lesch-Nyhan syndrome.* Dev Med Child Neurol 2005, 47(9): 636-9.

82. Pralong, E., Pollo, C., Coubes, P. et al. *Electrophysiological characteristics of limbic and motor globus pallidus internus (GPI) neurons in two cases of Lesch-Nyhan syndrome.* Neurophysiol Clin 2005, 35(5-6): 168-73.

83. Taira, T., Kobayashi, T., Hori, T. *Disappearance of self-mutilating behavior in a patient with Lesch-Nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. Case report.* J Neurosurg 2003, 98(2): 414-6.