



A Review on Lesch-Nyhan Syndrome: A Rare Inherited Disorder with Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency

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ABSTRACT

Lesch-Nyhan Disease (LND) is a rare X-linked recessive metabolic and neurological syndrome due to the deficiency of Hypoxanthine-guanine phosphoribosyltransferase (HPRT). LND is characterized by the overproduction of uric acid leads to gouty arthritis and kidney and bladder stones. The nervous system and behavioural disturbances are experienced in LNS patients. Abnormal involuntary muscle movements like dystonia, chorea and ballismus are the neurological disturbances and self injury like biting and head banging are the distinctive behavioural problems. Treatment is symptomatic and supportive and affected people don't survive first or second decade of life due to renal failure.

Keywords: Lesch Nyhan Syndrome, Hypoxanthine-guanine phosphoribosyltransferase, Gout, Juvenile Gout, Uric acid, Inheritance.

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Epidemiology and History

LND is thought to affect anywhere between 1 case per 235,000 and 1 case per 380,000 live births.³ Most ethnic groups have reported LND, with rates that are roughly equal across the board. Almost all patients are men due to the X-linked recessive form of inheritance. Although few female patients have been recorded to far, LND may affect females due to unusual genetic abnormalities. Most individuals seek medical care at a young age, typically before the age of 4.⁴

Lesch and Nyhan studied the Lesch-Nyhan syndrome in 1964; it is a rare heritable disorder of inborn faulty metabolism of purine. They looked at the two brothers who had neurobehavioral issues and hyperuricemia, and they suggested that this disorder involves motor impairment and self-injurious behaviour. Lesch-Nyhan syndrome affects 1 in 380000 people, and only men are affected by this condition.⁵ Since the X-linked recessive trait results in genetic mutation and the activity of an enzyme called hypoxanthine guanine phosphoribosyltransferase, it is passed on from parent to child (HGPRT). Purine overproduction, a metabolic disorder known as Lesch-Nyhan syndrome, is characterised by a markedly elevated amount of uric acid.⁶

Inheritance

Lesch-Nyhan syndrome is detected through inheritance. Lesch-Nyhan syndrome is an almost exclusively male condition that is caused by an X-linked recessive gene. Sons and daughters with either an affected father and an unaffected mother or an unaffected father and a carrier mother are at risk.⁷ Overproduction of uric acid and abnormalities in neurological function and behaviour are its defining features. Blood and urine contain uric acid, a waste product of regular chemical reactions. Gouty arthritis can be brought on by an accumulation of extra uric

INTRODUCTION

Lesch nyhan syndrome is also known as juvenile gout. It is a disorder of purine metabolism due to the deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT). It is a X-linked inheritance, caused by mutation in the HPRT gene. It is considered as secondary gout associated with inborn errors of metabolism leading to over production of uric acid and increased urinary excretion.¹

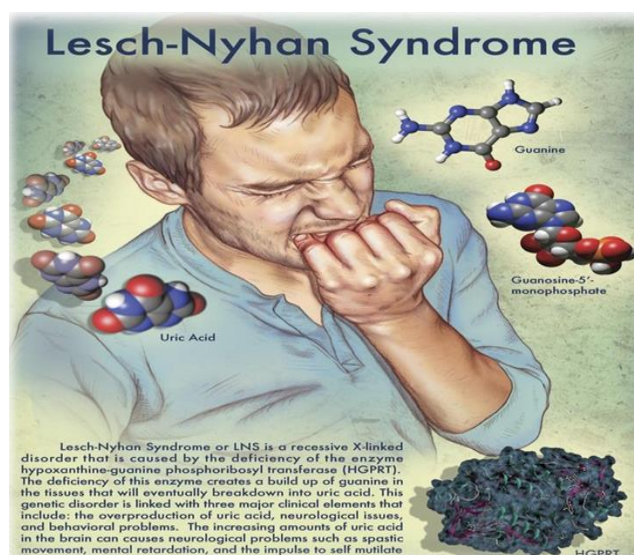


Figure 1: Lesch-Nyhan Syndrome (art design.rit.edu).²



acid under the skin that is discharged from the circulation (arthritis caused by an accumulation of uric acid in the joints). Stones in the kidneys and bladder can also be caused by uric acid buildup.⁸

Moreover, because the HPRT gene mutation is located on the X chromosome and the Lesch-Nyhan syndrome is only described in males, it is inherited as an X-linked recessive trait.⁹

The X-linked inheritance most critically established that the X-linked character cannot pass from the father to the son. The Lyon theory can be used to show that the mothers

with this disease are heterozygous and that the mosaics involve two cell cultures, one of which is completely normal and the other of which is completely wrong. Using the radio autographic approach, it is investigated whether the fibroblasts growing in skin cell populations were duplicated and whether HGPRT deficiency in the negative duplication could be seen.¹⁰ The HGPRT in the erythrocytes or leucocytes of the required heterozygote for this situation is distinct from the glucose-6-phosphate dehydrogenase (G6PD) deficiency where the transportation of enzyme in heterozygote is around 50%.

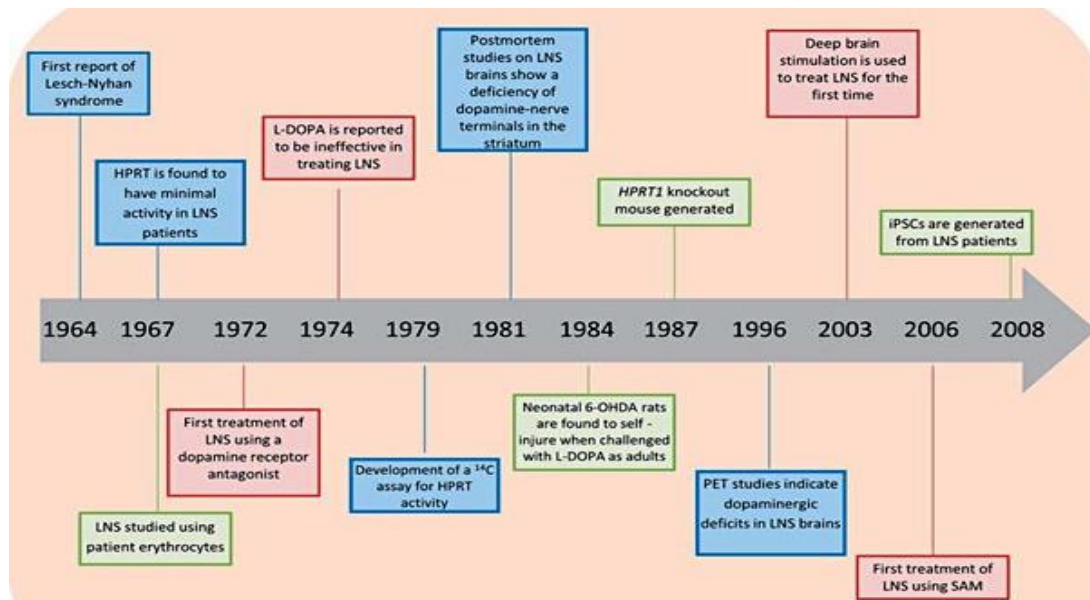


Figure 2: Schematic timeline of important milestones in the study of LNS. Studies relating to the underlying etiology of LNS, the treatment of LNS, and the generation of LNS models are highlighted in blue, red, and green, respectively.

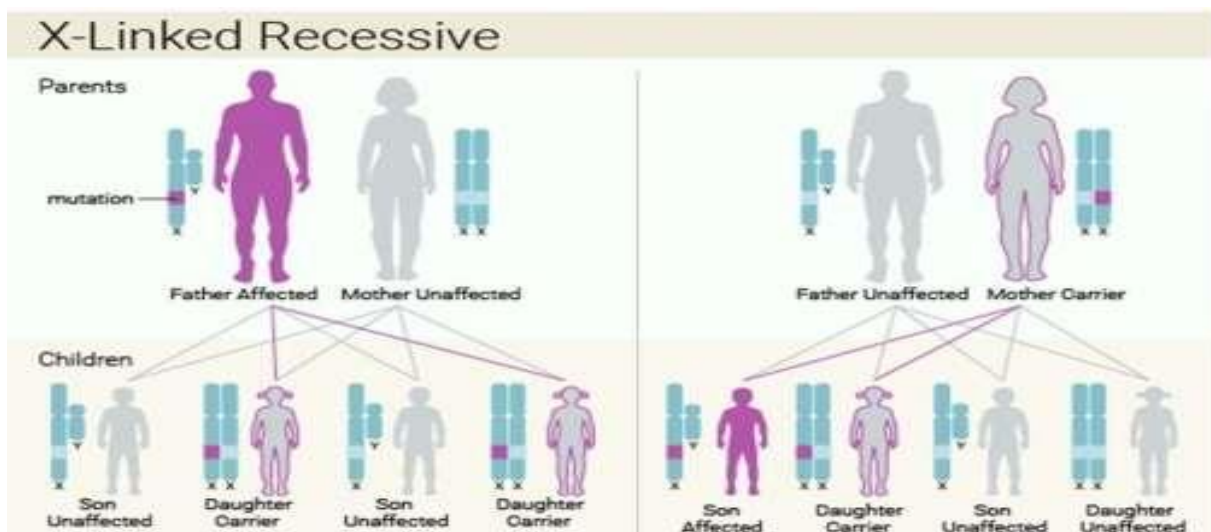


Figure-3: This condition is inherited in an X-linked recessive pattern. The gene associated with this condition is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

As a result, the halt of the X chromosome is not described as a random activity. It appears that the moms with Lesch-Nyhan syndrome have normal enzyme activity in their erythrocytes. Additionally, the blood-relative family of the two types of G6PD and HGPRT are separating, indicating that the females were heterozygous for G6PD. Because males only have one X chromosome, one altered copy of the gene is sufficient to induce this syndrome, whereas females are less likely to have two altered copies of the gene. This makes males more likely than females to experience this X-linked recessive disease.¹¹

It is verified that the patient's male father is not a carrier of the mutant gene and is not afflicted with the disease. The chance taken depends on the mother's carrier status. Each gestation from a carrier woman has a 50% probability of transmitting the HPRT1 variant. The daughters who receive the variation are used as carriers, and the sons who receive the variation will be influenced. Therefore, it may be said that a carrier mother has a one-fourth probability of having an afflicted son, a one-fourth chance of having a carrier daughter, and a fifty percent chance of having a normal son or daughter.¹²

Etiology

A mutation in the hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene, located at Xq26-q27 on the long arm of the X chromosome, results in LND.¹³ These are illustrations of the heterogeneous mutations, which also include point mutations and different types of substitutions, deletions, and insertions. Since certain tiny mutational hotspots have historically existed, it is generally accepted that the majority of mutations result in de-novo. Genotype-phenotype correlations don't necessarily mean that particular mutation sites are linked to particular disease symptoms. Less severe clinical manifestations (Lesch-Nyhan variations, LNV) are typically caused by mutations that are projected to leave some residual enzyme function.¹⁴

The HPRT1 gene mutations that cause Lesch-Nyhan syndrome. Making the enzyme hypoxanthine phosphoribosyltransferase-1 is guided by the HPRT1 gene. Purines, a sort of building material for DNA and its chemical cousin RNA, are recycled by this enzyme. Recycling purines makes ensuring that cells have an ample supply of the components needed to make DNA and RNA.¹⁵

Hypoxanthine phosphoribosyltransferase-1 is severely deficient or absent as a result of HPRT1 gene mutations that cause Lesch-Nyhan syndrome. Purines are broken down but not recycled when this enzyme is absent, resulting in excessively high levels of uric acid. Lack of the enzyme hypoxanthine phosphoribosyltransferase-1 is connected, for unclear reasons, to low levels of the chemical messenger dopamine in the brain.¹⁶ Movement issues and other characteristics of this condition may be related to dopamine deficiency since dopamine provides messages that assist the brain in controlling physical movement and emotional behaviour. The neurological and behavioural

issues that characterise Lesch-Nyhan syndrome are thought to be caused by a lack of hypoxanthine phosphoribosyltransferase-1.¹⁷

Some HPRT-1 gene mutation carriers produce some functioning enzyme. These people are alleged to have the Lesch-Nyhan variation. Self-injury is not one of the signs or symptoms of Lesch nyhan variation, which are frequently milder than those of Lesch nyhan syndrome.¹⁸

Pathogenesis

The recycling of hypoxanthine and guanine into their respective nucleotide pools is mediated by the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). Hypoxanthine and guanine are not recycled in the absence of HPRT; instead, they are broken down into uric acid. Along with the activation of de-novo purine synthesis, the diminished purine salvage significantly increases the generation of uric acid. However, average serum uric acid levels are kept in check by effective renal clearance, often increasing by less than a factor of two. The total renal excretion of uric acid in classic LND is usually four times higher than in controls. Chronic serum urate levels >7.0 mg/dL are linked to an increased risk of urate crystal deposition in tissues under the skin, such as joints and kidneys. Gouty arthritis, nephrolithiasis, and subcutaneous tophi may result from this if left untreated.¹⁹

One of the neurobehavioral characteristics of LND is a substantial decline in brain dopamine concentration in the basal ganglia, which is thought to be a key determinant of the hyperkinetic movement disorder, attention impairments, and aberrant behaviour.²⁰ Additionally, substantial abnormalities of the grey and white matter are linked to LND and LNV, which may offer crucial hints about the neurological underpinnings of the phenotype. Uncertainty exists regarding the precise relationship between HPRT deficit and dopamine dysfunction in LND.²¹ However, evidence points to a significant link between purine recycling pathways and the neurochemical integrity of the dopaminergic phenotype, and it has been suggested that HPRT plays a role in the processes of neurodevelopment.²² Although the dopamine deficiency, the impacts of dopamine replacement therapy are uneven and typically unhelpful, most likely as a result of the emergence of supersensitive dopamine receptors and other neuroplastic alterations. Other side effects of certain patients' corticospinal motor system dysfunction include spasticity and hyperreflexia. Myelopathy brought on by repeated, jerky, unconscious movements of the neck may be the cause of this.²³

Clinical Manifestations

The symptoms of Lesch-Nyhan Syndrome can be broadly categorised in to 3 major categories²⁴:

Symptoms associated with uric acid accumulation Sodium urate crystals in neonates' urine, which cause diapers to look like "orange sand," are among the symptoms of uric acid buildup.



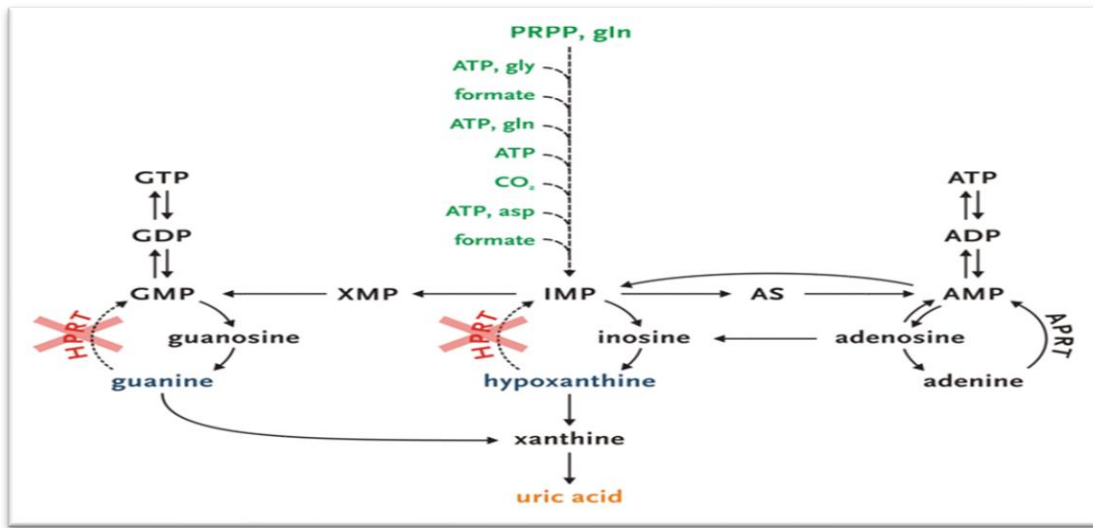


Figure-4: The role of hypoxanthine-guanine phosphoribosyltransferase (HPRT) in the grand scheme of purine metabolism

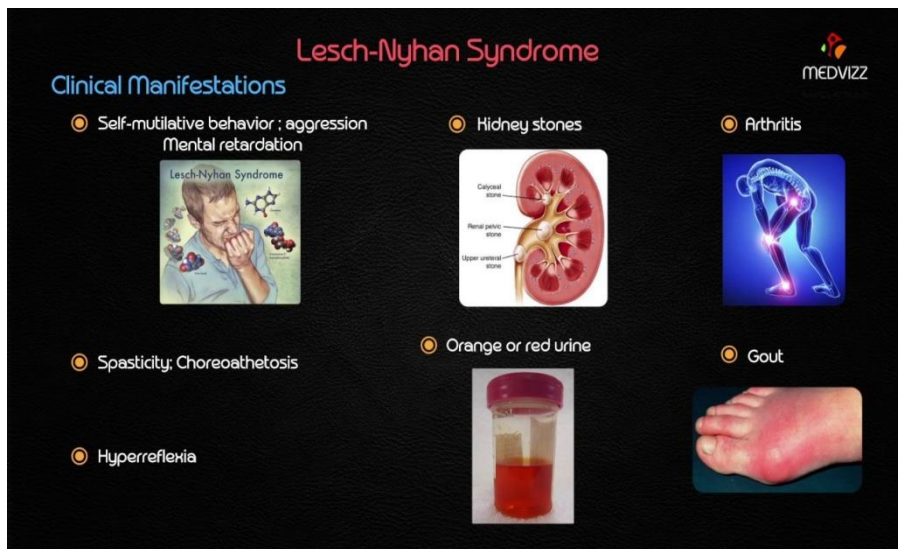


Figure 5: Clinical manifestations of Lesch-Nyhan syndrome.

The development of kidney and bladder stones, pee with blood, vulnerability to recurrent urinary tract infections joint discomfort and edoema, Sodium urate buildup in cartilage tissue (Gout). Tophi, or ear bumps, might result from this.

Neurological symptoms Repetitive motions, such as grimacing, rising shoulders, and moving figures, together known as chorea, are among the neurological signs. Low muscle tone and muscle contraction (dystonia) (hypotonia), newborns' inability to hold their heads up, being unable to sit straight, standing and walking difficulties, Speech issues (dysarthria), failure to meet developmental milestone.

Behavioural symptoms: Self harm includes biting, scratching, and hitting one's head against objects, screaming, throwing up, and becoming aggressive.

Additional symptoms like intellectual disability and low weight gain.²⁵

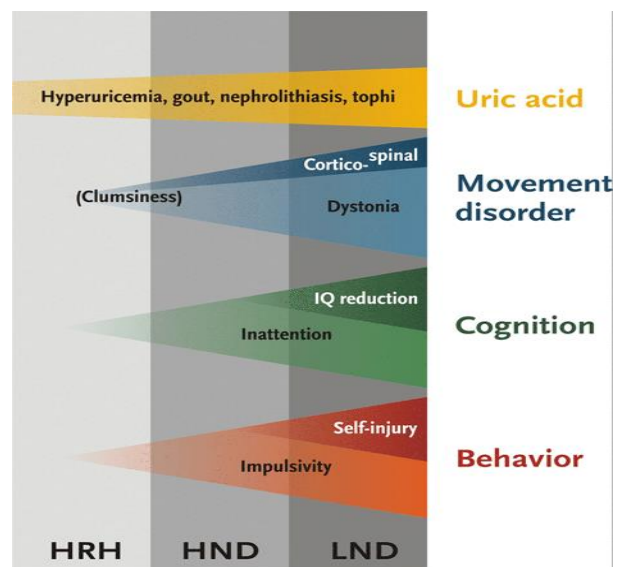


Figure-6: Phenotypic spectrum associated with hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. HND: HPRT-related neurologic disease; LND: Lesch-Nyhan disease.

DIAGNOSIS

Diagnosis Test	Result
serum uric acid level	Elevated
24-hour urinary uric acid excretion	Elevated
hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene analysis	Mutation in the coding region of the HPRT gene
HPRT enzyme activity	Reduced; typical values (% of normal): classic LND <1.5%; hyperuricemia with neurologic dysfunction (HRND) <8%; HPRT-related hyperuricemia (HRH) ≥8%
Brain MRI	May reveal mild loss of brain volume

A careful examination of the patient and a detailed case history can both help to diagnose Lesch Nyhan Syndrome. In order to find elevated uric acid levels, blood and urine tests are performed. Microcytic anaemia may also be found during blood tests.²⁶

Clinical examinations are conducted to evaluate cognitive abilities, behavioural issues, and neurological functioning. In addition to the usual clinical signs, the doctor might be able to elicit spasticity and heightened reflexes. Physical examination to determine growth may reveal testicular atrophy, delayed growth and development, learning challenges, and absent or delayed puberty.²⁷

Lesch Nyhan Syndrome is often diagnosed based on its three key features: excessive production of uric acid, neurological damage, and behavioural issues. Genetic testing and enzyme activity studies can be used to determine the precise diagnosis.

Molecular genetics: Learn more about the HPRT1 gene for information on the molecular abnormalities associated with Lesch-Nyhan syndrome.²⁸

Treatment

Patient Group	Tx Line	Treatment
All patients	1st	Allopurinol By significantly lowering serum acid levels, allopurinol lowers the risk of urologic and articular problems brought on by hyperuricemia. Allopurinol prevents the formation of uric acid from xanthine and hypoxanthine. ³² Doses must be modified for renal impairment in order to maintain uric acid levels in the high-normal range.

Genotype/Phenotype Correlations:

Lesch-Nyhan syndrome patients have varying degrees of illness severity, and there is an inverse correlation between clinical severity and HPRT1 enzyme activity as determined in intact cells. Less than 1.5% of normal HPRT enzyme activity is present in intact cultured fibroblasts in patients with classic Lesch-Nyhan disease, the most severe and prevalent variant. Patients with Lesch-Nyhan variations, or partial HPRT insufficiency, have HPRT1 enzyme activity ranging from 1.5 to 8.0%. Neurologically identical to individuals with Lesch-Nyhan illness, people with the intermediate variant type known as the "neurologic variant" lack self-injurious behaviours and have normal or almost normal IQ. The individuals with the variant type who are least affected have residual HPRT1 enzyme activity above 8%; their only symptoms, gout, hematuria, and nephrolithiasis, are all related to hyperuricemia.²⁹

Management

Given that Lesch Nyhan Syndrome is a genetic condition, there is no known treatment for it. However, some drugs may be used to lessen symptoms,

1. Allopurinol to treat gouty arthritis or elevated uric acid levels.
2. Drugs like gabapentin, haloperidol, or diazepam are occasionally used to treat spastic and associated conditions as well as behavioural difficulties.
3. Urinary stone treatment is done with the proper intervention.
4. For issues related to the muscles and joints, surgery may be an option.

A normal healthy diet and activity is generally advised. It is important to ensure proper hydration and have increased intake of fluids to reduce the risk of urinary stones.³⁰

To stop head bashing and biting from causing serious damage, physical constraints can be necessary. Managing behavioural and cognitive issues may benefit from rehabilitative therapy such as behaviour modification approaches.³¹



Patient Group	Tx Line	Treatment
		Primary Options: Allopurinol: Children should take 10 mg/kg/day of allopurinol orally in 2-3 divided doses, with the dosage adjusted to keep uric acid levels in the high-normal range, with a daily maximum of 800 mg. Adults should take 100-600 mg/day orally in 2-3 divided doses, with the dosage adjusted to keep uric acid levels in the high-normal range. ³³
	Plus	Generous hydration To flush out the Allopurinol, oxypurine hypoxanthine and xanthine, and the Allopurinol metabolite oxypurinol, which may also result in (radiolucent) kidney stones, ample hydration is necessary at all times. Typically, it is advised to consume 2 to 2.5L of total fluid per 1.73 m ² of body surface area (BSA). A goal urine volume of at least 1.5 L, ideally 2 to 2.5 L, has been suggested for adults. The objective is to reduce the amount of uric acid in the urine and to prevent dehydration when experiencing fever or vomiting attacks (e.g., on hot days). ³⁴
	Plus	Physical therapy to reduce contractures Physical treatment is typically helpful to avoid contractures and maintain overall health.
With dystonia, chorea, and/or ballismus	Adjunct	Botulinum toxin injection. Botulinum toxin injections can be used to treat the symptoms of severe dystonia, such as enhancing hand function or preventing contractures. The dosage is determined by the level of dystonia, the muscle being injected, and the doctor's personal preferences. ³⁵ Primary Options Botulinum toxin type A: consult specialist for guidance on dose
With spasticity	Adjunct	Muscle relaxant and/or benzodiazepine If spasticity is an issue, a muscle relaxant such baclofen or dantrolene can be administered. A benzodiazepine and a muscle relaxant are frequently taken together. Additionally, benzodiazepines offer the benefit of lowering anxiety, which is known to worsen the extrapyramidal and behavioural symptoms. Primary Options Baclofen : Children should seek medical advice before taking baclofen; adults should start with 5 mg three times day and titrate up to a maximum of 70 mg per day depending on their reaction. or Dantrolene dosage for children is 1 mg/kg/day given orally in 3–4 split doses, and for adults is 25 mg/day given orally initially in divided doses, and for adults the maximum dose is 400 mg/day. -- AND/OR -- Diazepam: For adults, 2-10 mg orally three to four times per day; for children, 0.12 to 0.8 mg/kg/day.
With behavioral abnormalities	Plus	Positive reinforcement for desired behaviours The best way to cope with challenging behaviours is to realise that they are out of the patient's control, involve the patient in an active setting, reinforce desirable behaviours, and intentionally ignore unpleasant ones. Feeling understood is really important for many patients. ³⁶ The management of behavioural problems in LND has not been consistently proven to be beneficial with drugs, and they also do not respond consistently to traditional psychological therapy. Unwanted behaviour is typically increased by negative reinforcement. ³⁷



Patient Group	Tx Line	Treatment
	Adjunct	Measures to counter self-injurious behavior The best way to deal with self-injury is to include the patient in physical activity while purposefully disregarding the self-destructive behavior. Self-injury may rise as a result of negative reinforcement. A physical constraint of some kind, such as arm splints, limb restraints, or protective gloves, is required for the majority of patients. When less drastic methods are unsuccessful, tooth extractions are required to stop biting. Reachable hard things include wheelchairs and soft cushioning. ³⁸
With Renal stones	Plus	Increased fluid intake and urine alkalinisation The first choice is potassium citrate. Urine alkalinization with potassium citrate being the chosen treatment and increased fluid intake are typically sufficient to treat small urate stones. In order to avoid long-term renal problems, treatment is necessary.
	Adjunct	Lithotripsy or surgery Lithotripsy or surgery may be necessary for large stones and oxypurine stones, however the latter is trickier to remove. To prevent long-term renal problems, treatment is necessary.

Prevention

The most crucial medical intervention is primary prevention because there aren't any efficient treatments for the neurobehavioral symptoms of LND at the moment. This includes establishing the carrier status of women in these families and providing genetic counselling to families with LND patients. If the family would contemplate terminating the pregnancy in the event of an impacted pregnancy, female carriers should have all subsequent pregnancies evaluated with pre-implantation or prenatal diagnostics. Regarding family planning, appropriate advice should be given.³⁹

CONCLUSION

An uncommon self-mutilating condition called LND is caused by a lack of the HPRT enzyme. The second most prevalent inborn metabolic disease is this one. In LND patients, there are no established techniques for preventing self-mutilation. Based on the closure observation, appropriate preventive strategies must be devised for each particular patient.

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