ABSTRACT
Lesch-Nyhan syndrome (LNS) is a rare inborn error of purine metabolism, passed down as an X-linked, or sex-linked trait. People with this syndrome are missing or severely lacking an enzyme called hypoxanthine guanine phosphoribosyltransferase 1 (HPRT). The body needs this substance to metabolize uric acid. Without this enzyme, uric acid builds up in the central nervous system, kidneys, and other areas of the body. The three main features of the disease are Excessive production of uric acid, Neurological problems and Behavioural disorders. The first symptom of Lesch-Nyhan syndrome may be orange-colored crystal-like deposits, caused by increased uric acid in the urine. The diagnosis of LNS may be confirmed by a thorough clinical evaluation, including a detailed patient history and specialized blood tests. Children with this disorder have abnormally high concentrations of uric acid in the blood. The absence of the enzyme HPRT in cells from any tissue confirms the diagnosis. Carrier testing is possible using molecular genetic testing. Prenatal diagnosis and preimplantation genetic diagnosis are possible if the disease-causing HPRT1 gene mutation has been identified in an affected family member. Prenatal diagnosis can also be done by enzyme analysis. No specific treatment exists for Lesch-Nyhan syndrome. Gout can be treated with allopurinol, reduces uric acid levels. However, treatment does not improve the neurological outcome. Few treatments have proven consistently helpful for the neurologic or behavioral difficulties. Behavioral abnormalities are best managed by a combination of behavioral modification techniques and medications.

KEYWORDS: Lesch–Nyhan syndrome (LNS), hypoxanthine guanine phosphoribosyltransferase 1 (HPRT), uric acid, orange sand, gene mutation.
INTRODUCTION
Lesch–Nyhan syndrome (LNS), also known as Nyhan's syndrome and juvenile gout, was first recognized and clinically characterized by Michael Lesch and William Nyhan, who published their findings in 1964. Within three years, the metabolic cause was identified by J. Edwin Seegmiller and his colleagues at the NIH.

LNS is an uncommon genetic disorder that involves a hypoxanthine-guanine phosphoribosyltransferase deficiency. Hypoxanthine-guanine phosphoribosyltransferase is an enzyme in the purine salvage pathway. A purine is a protein found in normal healthy body tissue that make the body’s blueprint. They are also important for the metabolism of RNA and DNA that make up our genetic code, this mutation cause uric acid build up, neurological disability, and self injury.

As an X-linked recessive disorder it affects almost exclusively males, with female cases being a rarity.

EPIDEMIOLOGY
The reported worldwide prevalence of Lesch-Nyhan disease is 1 case per 380,000 population. The prevalence of the disease is estimated to be 1/380,000 live births in Canada, and 1/235,000 live births in Spain. HPRT deficiency is inherited as a recessive X-linked trait. Thus, males are generally affected and women are generally asymptomatic carriers.

CLINICAL FEATURES
There is a spectrum of clinical features associated with HPRT deficiency. The three main features of the disease are
- Excessive production of uric acid.
- Neurological problems, especially general learning disability, spastic cerebral palsy and choreoathetosis.
- Behavioural disorders

Over production of uric acid
- Increased production of uric acid leads to precipitation of uric acid crystals in certain areas of the body such as
  - joints, where they cause gouty arthritis,
urogenital system, where they lead to a sandy sludge or stones in the urinary collecting system.

- subcutaneous tissues where they form visible masses known as tophi

- These materials can also obstruct the flow of urine, leading to renal failure.

**Nervous system impairment**

The periods before and surrounding birth are typically normal in individuals with LNS. The most common presenting features are:

- Abnormally decreased muscle tone (hypotonia) and developmental delay, which are evident by three to six months of age.

- Affected individuals are late in sitting up, while most never crawl or walk.

- Lack of speech is also a very common trait associated with LNS.

- Irritability is most often noticed along with the first signs of nervous system impairment.

- Within the first few years of life, extrapyramidal involvement causes abnormal involuntary muscle contractions such as loss of motor control (dystonia) writhing motions (choreoathetosis), arching of the spine (opisthotonus).

- Signs of pyramidal system involvement, including Spasticity, overactive reflexes (hyperreflexia), extensor plantar reflexes

**Self-injuring behavior**

- Persons affected are cognitively impaired and have behavioral disturbances that emerge between two and three years of age.

- Patients show patterns of

- recurrent self-injury, especially self-biting.

- Biting of tongue and lips

- Finger biting and head banging

- Patients also exhibit other behaviors such as

- impulsive acts of aggression

- spitting

- Use of foul or sexually charged language.

- Vomiting

- coprolalia
Some patients affected by LND exhibit other problems: an asymptomatic macrocytic anemia is common. Gastroesophageal reflux and recurrent emesis can be severe enough to lead to malnutrition. Finally, exceptional patients are affected by a milder phenotype in which some aspects of the clinical phenotype are attenuated or even absent – these patients are known as the Lesch-Nyhan variants.\textsuperscript{[8-10]}

\begin{figure}[h]
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\caption{Self injuring behavior; A)Bitting of hand, B)biting of nail, C)Biting of lip, D)Uric acid deposition, Swollen and inflammation of joint}
\end{figure}

\textbf{ETIOLOGY}

Lesch-Nyhan disease and its variants are caused by mutations in the HPRT gene on the X chromosome.\textsuperscript{[11]} The mutations are heterogeneous, with more than 600 different ones documented, including single base substitutions, deletions, insertions, or substitutions.\textsuperscript{[12,13]}

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The HPRT gene has 9 exons, with the coding region depicted as light gray boxes. Genetic mutations in Lesch-Nyhan disease and its variants are heterogeneous and include point mutations leading to amino acid substitution (yellow circles), point mutations leading to premature stop (red squares), insertions (blue triangles), deletions (white lines), and other more complex changes (not shown).

PATHOPHYSIOLOGY

As in other X-linked diseases, males are affected because they only have one copy of the X chromosome. In Lesch–Nyhan syndrome, the defective gene is that for hypoxanthine-guaninephosphoribosyltransferase (HPRT), a participant in the 'recycling' of purine nucleotides. Female carriers have a second X chromosome, which contains a "normal" copy of HPRT, preventing the disease from developing, though they may have increased risk of hyperuricemia.

A large number of mutations of HPRT are known. Mutations that only mildly decrease the enzyme's function do not normally cause the severe form of LNS, but do produce a milder form of the disease which still features purine overproduction accompanied by susceptibility to gout and uric acidnephrolithiasis.

Purines are heterocyclic aromatic organic compounds that are components of DNA and RNA; they are also involved in energy production, signal transduction with in cells, and neurotransmitters. Purines and pyrimidine bases are normally recycled by salvage pathways. This process is a single reaction catalyzed by hypoxanthine-guanine phosphoribosyltransferase. In this reaction, free xanthine and guanine react with 5'-
phosphoribosyl-1-pyrophosphate (PRPP) to produce guanine-monophosphate (GMP) adenine-monophosphate (AMP) plus diphosphate, PPi.

When the salvage pathway fails, purines build up and degradation of purines occurs. Degradation of purines occurs in a step by step manner. The first step is removal of a phosphate by the enzyme 5’-nucleotidase. This occurs in both guanine monophosphate and adenine-monophosphate. This results in guanosine and adenosine.

Here the pathway splits into two and Adenosine is deaminated by adenosinedeaminase to produce inosine. Inosine and guanosine are hydrolyzed to guanine and hypoxanthine by nucleosidase. Guanine is deaminated by guanine deaminase while hypoxanthine is oxidized to xanthine by the combination of the two products, by xanthine oxidase. Further oxidation results in the formation of uric acid.[14]

Due to increased availability of PRPP, the rate-limiting step in de novo synthesis is decreased, making de novo synthesis a quicker process.

The rate limiting step is shown below, and is the second step in the process. Because of the constant degradation of the purines there is no negative feedback inhibition of the PRPP amidotransferase, which results in constant AMP and GMP formation.[16]

**DIAGNOSIS**

The diagnosis of HPRT deficiency must be supported by clinical, biochemical, enzymatic and molecular data.
Clinical and Biochemical diagnosis

- HPRT deficiency should be suspected in patients with hyperuricemia and uric acid overproduction with or without neurological impairment.
- Nephrolithiasis and obstructive nephropathy are common early manifestations in patients with partial HPRT deficiency.
- Neuro imaging tests such as computing tomography (CT) and magnetic resonance imaging (MRI) may show atrophic non-specific changes.
- The urinary uric acid/creatinine ratio can be employed as a screening test for inherited disorders of purine metabolism, but the values should be evaluated based on the age of the patient. Normal values for the urinary uric acid/creatinine ratio are below 1.0 after age 3-years.
- Mean plasma concentrations of urate, hypoxanthine, and xanthine, and their urinary excretion rates, are markedly elevated in HPRT-deficient patients.

Enzymatic diagnosis

- HPRT deficiency must be confirmed by enzymatic determinations.
- To better characterize the HPRT deficiency, enzyme activity can be measured in intact cells (erythrocytes or fibroblasts).
- A correlation was found between residual HPRT activity in intact erythrocytes and fibroblasts and neurological involvement, although values may overlap for patients with very different phenotypes.

Molecular diagnosis

- **Gene.** HPRT1 is the only gene, known to be associated with Lesch-Nyhan syndrome.

Differential diagnosis

- Complete HPRT deficiency-associated psychomotor delay must be differentiated from cerebral palsy.
- Self-injurious behaviour is also present in other conditions such as idiopathic mental retardation, autism, Tourette syndrome, Cornelia de Lange syndrome, severe psychiatric alterations, etc.
- In partial HPRT deficiency, differential diagnosis should explore other possible causes of hyperuricaemia and gout.
• Elevated excretion of uric acid as an indication of purine overproduction is an important hallmark in the differential diagnosis. Other causes of hyperuricemia with purine overproduction include PRPP synthetase superactivity and glucose 6-phosphate deshydrogenase deficiency.

Antenatal diagnosis
• Prenatal diagnosis for Lesch-Nyhan syndrome can be performed with amniotic cells obtained by amniocentesis at about 15–18 weeks' gestation, or chorionic villus cells obtained at about 10–12 weeks' gestation. Both HPRT enzymatic assay and molecular analysis for the known disease-causing mutation can be performed.[15]

TREATMENT
Management of hyperuricemia
The overproduction of uric acid must be controlled to reduce the risk for nephrolithiasis, urate nephropathy, gouty arthritis, and tophi.

Allopurinol: It inhibits the metabolism of hypoxanthine and xanthine to uric acid by the enzyme xanthine oxidase, is generally effective in limiting hyperuricemia and its consequences. The dose is titrated with the goal of bringing serum uric acid levels into the normal range. Febuxostat is a newer option for patients who cannot tolerate allopurinol.

Management of neurological dysfunction
• Spasticity can be helped with a combination of baclofen and benzodiazepines. Diazepam is most commonly used. They may also help some of the extrapyramidal features.

Management of behavioral problems
• Management of the behavioral problems, particularly the self-injurious behavior, can be very difficult.
• Behavioral problems are best managed with a combination of behavioral-modification techniques and medication.
• Behavioral extinction methods with positive reinforcement are most beneficial; techniques involving negative reinforcement are not helpful and may even exacerbate the behavior problems.
• Neuroleptics are sometimes used when problems are particularly severe, although long-term use is discouraged because of side effects.
Dental, Orthopedic, and Other interventions

- Dental extraction may be the only procedure for preventing serious tissue injury if self-injurious biting cannot be controlled with behavioral and/or medical therapy.
- Orthopedic intervention is often required for management of the consequences of the neurologic disorder. Procedures may be required for release of contractures, reduction of subluxed joints, or stabilization of spinal deformity.
- Nephrolithiasis may require surgical intervention for extraction of stones or relief from urogenital obstruction.
- Some studies have provided a promising suggestion that deep brain stimulation surgery may be useful for controlling both dystonia and self-injury.

TREATMENT UNDER INVESTIGATION

- Recent studies suggesting that gabapentin and carbamazepine may help attenuate self-injury and other behavioral disturbances have not been confirmed in a long-term study.
- Other treatments under investigation for the management of self-injurious behavior are local injections of botulin toxin, deep brain stimulation in globus pallidus or dopamine replacement therapy, but they need to prove to be efficacious and safe in the long-term management of these patients.

CONCLUSION

Compared to other disease, lesch nyhan syndrome is a rare hereditary disorder that affects body’s ability to breakdown and build purines and affects children at a very young age. Children with this disease get kidney stones, they cannot control their muscles, and they develop an irresistible urge to try to hurt themselves. Many patients have variations in severity. All patients however, have one thing in common, the lack of the HPRT enzyme. Research has lead to the discovery of a genetic sequence that results in a defective enzyme, but researchers are still unsure how this leads to the neurological and behavioral problems that are the hallmark of the disorder. Treatments as simple as wearing oven mitts and as complicated as electrical wiring in the brain have been used to help LNS patients, but no cure for the syndrome seems in sight.

REFERENCES