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LESCH-NYHAN SYNDROME: PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, AND EMERGING THERAPEUTIC APPROACHES

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Abstract

Lesch-Nyhan Syndrome is a rare X-linked recessive genetic disorder caused by mutations in the HPRT1 gene, which codes for the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT). This enzyme is necessary for the purine salvage pathway, which recycles purines to keep the cells' nucleotide equilibrium. Excess uric acid and other serious neurological and behavioral issues are caused by a lack of HPRT activity. Clinical signs of Lesch-Nyhan Syndrome include hyperuricemia, gout, kidney stones, cognitive impairment, motor dysfunction (including stiffness and dystonia), and a characteristic conduct that is self-harming, such as biting one's lips or fingers. The condition primarily affects men due to its X-linked inheritance pattern. Since there is currently no known cure for Lesch-Nyhan Syndrome, supportive care is the cornerstone of treatment to lower neurological symptoms and regulate uric acid levels. Current research is looking into gene therapy and enzyme substitution as potential treatment modalities. Early diagnosis using enzymatic assays and genetic testing is essential for family counselling and disease management. Early diagnosis using enzymatic assays and genetic testing is essential for family counselling and disease management. Treatment is centered on managing symptoms because there is currently no cure. Neurological and behavioral problems are treated with medicine and supportive care, while uric acid levels are controlled with allopurinol. Purine metabolism and the neurological effects of metabolic dysregulation have been better understood because of our growing understanding of the molecular groundwork of Lesch-Nyhan Syndrome.

INTRODUCTION

Michael Lesch and William Nyhan initially described Lesch-Nyhan Syndrome (LNS), a rare X-linked recessive genetic disorder, in 1964. The long arm of X chromosome (Xq26–q27) contains the HPRT1 gene, which codes for the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT). Mutations in this gene cause it (see Reisz et al., 2023; Wang et al., 2022). According to Whole Exome Sequencing Facilitates Early Diagnosis (2022), this enzyme is necessary for the purine salvage pathway, a biological process that transforms purines (adenine and guanine) into nucleotides, which are the building blocks of DNA and RNA**.** Partial or total HPRT deficiency disrupts this process in LNS, leading to hyperuricemia, or an accumulation of uric acid in the blood and tissues, which exacerbates the condition's neurological and behavioral symptoms (Reisz et al., 2023; HPRT1

Frontier in Medical & Health Research

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Deficiency Induces Alteration of Mitochondrial Energy Metabolism, 2023). Clinically, LNS typically shows up in infancy as developmental delays and hypotonia, or weak muscle control. As the kid grows older, more severe motor symptoms like dystonia, choreoathetosis, and spasticity manifest (S Marwaha et al., 2022; Whole Exome Sequencing Facilitates Early Diagnosis, 2022). Self-harming behaviors, which usually begin between the ages of two and three, are a defining and diagnostically significant feature of LNS. Examples of these behaviors include biting one's lips, fingers, or other body parts. Along with cognitive impairment, behavioral abnormalities like impulsivity, aggression, and obsessive-compulsive behaviors are also common. High levels of uric acid can also lead to gout, kidney stones, hematuria, and renal failure. Males are more likely to be affected by LNS due to its X-linked inheritance pattern, while female carriers typically do not exhibit any symptoms (Drishti Valechha et al., 2025).

There is currently no known treatment for Lesch-Nyhan Syndrome. Lowering uric acid levels with medications like allopurinol, controlling neurological symptoms with antispasmodics or muscle relaxants, and promoting behavior are the major objectives of care. Self-harm prevention or management often requires a multidisciplinary approach that may include behavioral therapy, physical constraints, and in some cases, dental extractions. Ongoing research into enzyme replacement and gene therapy has made future treatment alternatives feasible (Valechha D., Jyotishi C. & Patel M.,2025; World Academy of Science). Recent genetic research has shed light on the molecular diversity underlying LNS. A 2022 study of eight Chinese patients revealed a clinical variety in the manifestation of LNS and discovered numerous new mutations in HPRT1 (including frameshift and nonsense mutations, which were mainly concentrated in exon 3) (see detailed genetic and clinical analysis, 2022). A more recent multi-omics study of red blood cells from three pediatric LNS patients (with a novel S162N HPRT1 variant) revealed unexpected metabolic changes, including the accumulation of glycolytic intermediates, long chain acylcarnitine, altered lipid profiles (elevated unsaturated phosphatidylcholines, decreased free choline), and decreased intracellular trace metals (iron, zinc, selenium, potassium) (Reisz et al., 2023). These findings suggest that beyond purine salvage insufficiency, there may be more widespread disturbances in lipid metabolism, cellular ion balance, redox homeostasis, and membrane/protein alterations in the LNS, which may result in novel therapeutic strategies or the development of biomarkers (Reisz et al., 2023). On the therapeutic front, current assessments suggest a few additional aspects, while the standard treatment remains symptomatic (e.g., limiting dietary purines, staying hydrated, and using allopurinol to reduce uric acid levels). S-adenosylmethionine (SAMe), for example, has been shown to help in the neurological and behavioral domains in certain people when tolerated. Research is still at the experimental stage, but potential treatments such as gene therapy, enzyme replacement, and neuroprotective drugs are being explored (Charmi Jyotishi et al.,2025; Symptomatic care and novel therapeutic directions).

Lesch-Nyhan Syndrome causes

In Lesch-Nyhan Syndrome, hypoxanthine-guanine phosphoribosyltransferase (HPRT) is either completely absent or impaired due to abnormalities in the HPRT1 gene (Reisz et al., 2023). The purine salvage system is disrupted by this genetic abnormality, resulting in metabolic and neurological problems.

Genetic lesion and relationships

LNS is hereditarily caused by either hylomorphic variants that retain residual activity and result in attenuated manifestations or loss-of-function variants in HPRT1 (nonsense, frameshift, massive deletions, splice-site mutations). The catalog of pathogenic HPRT1 variants has been further expanded by large recent cohorts and case series, which demonstrate that residual enzymatic activity broadly correlates with clinical severity, hylomorphic alleles cause variant forms with milder neurobehavioral features, while null alleles produce classic LNS (severe motor dysfunction, profound self-injury) (Li et al., 2022; Fang et al., 2024; AlBakheet et al., 2023). Affected females due to de novo mutations and skewed X-inactivation are among the several private and de novo variants highlighted by recent case reports and exome investigations (AlBakheet et al., 2023; Zheng,

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2025). Nowadays, a lot of people employ clinical genetic testing (targeted sequencing or WES) for early diagnosis, especially when hypotonia and hyperuricemia appear in infancy (Fang et al., 2024).

Beyond uric acid: systemic metabolic disruption

While the most obvious biochemical effect is hyperuricemia, multi-omics and cell-model studies conducted in recent years show that HPRT deficiency results in more extensive metabolic abnormalities. The accumulation of glycolytic intermediates upstream of pyruvate kinase, increased long-chain acylcarnitine, altered phosphatidylcholine species (↑ unsaturated PCs; ↓ free choline), and decreased intracellular trace metals (Fe, Zn, Se, K) were all observed in an RBC multi-omics study of pediatric siblings with an S162N HPRT1 variant. These findings suggested disruptions in glycolysis, lipid metabolism, redox balance, and ion homeostasis (Reisz et al., 2023). These metabolic anomalies imply that systemic metabolic reprogramming is triggered by loss of HPRT activity and cannot be reversed by uric-acid-lowering treatment alone (Reisz et al., 2023).

Neurodevelopmental vulnerability

The mechanistic proof that HPRT deficiency disproportionately affects dopaminergic progenitors and midbrain dopaminergic lineage development has been a significant breakthrough in the last five years. HPRT-deficient dopaminergic progenitors have diminished differentiation potential, altered metabolic programming (reduced glycolysis and oxidative phosphorylation efficiency), increased shunting into the pentose-phosphate pathway, loss of RHEB, and decreased mTORC1 signaling, according to human pluripotent stem-cell models and isogenic CRISPR knockouts. These alterations are likely to result in lifelong dopamine deficits (Bell et al., 2021; Boissart et al., 2023). Importantly, these developmental metabolic defects favor a developmental (impaired formation/function) rather than a purely degenerative model of dopaminergic dysfunction, which helps to explain long-standing clinical observations of markedly reduced dopamine in the basal ganglia as well as the distinctive motor and behavioral phenotype (Bell et al., 2021).

Integrated mechanistic hypotheses

According to recent data, HPRT1 loss leads to an integrated model in which:

1. Proliferating neural progenitors experience nucleotide-pool imbalance and stress (increasing demand on de novo synthesis pathways).
2. Energy-metabolism reprogramming and redox stress, which primarily affect metabolically vulnerable dopaminergic lineages.
3. Disruption of signaling pathways (e.g., reduced RHEB/mTORC1 activity) impairs neuronal differentiation.
4. Systemic membrane, lipid, and ion-homeostasis changes may alter synaptic and neuronal physiology (Bell et al., 2021; Reisz et al., 2023).

These mechanisms are not mutually exclusive and likely act in concert to produce the combined metabolic, motor, and behavioral phenotype of LNS.

Cellular and animal models supporting causation

Human embryonic stem cell sublines with HPRT deletions, CRISPR HPRT knockouts, and iPSC-derived neuronal models have all been created and utilized to screen for small-molecule rescue candidates and investigate pathophysiology (Sutcliffe et al., 2021; Ruillier et al., 2020; Boissart et al., 2023). Although there are significant delivery and safety challenges in clinical translation, these platforms have found metabolic rescue drugs in vitro and demonstrated proof of principle that gene-editing (base-editing or prime-editing) can fix specific HPRT1 mutations in patient-derived cells (Jang et al., 2023).

Clinical consequences of mechanistic insights

Understanding that LNS is driven by developmental dopaminergic vulnerability and broad metabolic dysregulation reframes therapeutic priorities, while allopurinol and uric acid lowering are essential to prevent gout and renal complications, they do not address core neurodevelopmental defects. Translational efforts now focus on three complementary approaches:

1. Restoring HPRT function through genetic correction or enzyme replacement.
2. Supporting energy/redox homeostasis during development through metabolic and neuroprotective strategies.

Frontier in Medical & Health Research

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3.Managing symptoms and behavior to prevent self-harm and enhance quality of life (Bell et al., 2021; Reisz et al., 2023; Jang et al., 2023).

Jinnah (2020) claims that Lesch–Nyhan Syndrome (LNS), an X-linked recessive neurodevelopmental disorder, is caused by pathogenic mutations in the HPRT1 gene, which encodes hypoxanthine-guanine phosphoribosyltransferase (HPRT), an essential enzyme in the purine salvage pathway. Purine bases can be recycled, and de novo purine synthesis and degradation to uric acid are reduced because HPRT catalyzes the conversion of guanine to guanosine monophosphate (GMP) and hypoxanthine to inosine monophosphate (IMP). The traditional metabolic signature of LNS, hyperuricemia and purine-pool imbalance, is caused by a loss or severe shortage of HPRT activity (Bell et al., 2021; Reisz et al., 2023).

Table No. 01: Mechanisms to Clinical Outcomes of Lesch-Nyhan Syndrome

Mechanistic Insight	Pathophysiological Outcome	Clinical Consequence
HPRT1 Gene Mutation	Impaired purine salvage, excess uric acid	Hyperuricemia, leading to gout and kidney stones
Dopaminergic dysfunction in basal ganglia	Reduced dopamine in motor and behavioral circuits	Dystonia, choreoathetosis, and self-injurious behavior (SIB)
Loss of inhibitory control in neural pathways	Abnormal impulse regulation	Compulsive behavior especially self-harm

Clinicopathological Features of LNS

LNS exhibits a variety of neurological and behavioral symptoms in addition to the typical metabolic indications of low body weight, gout, renal calculi, and renal failure. Spasticity, choreoathetosis, dystonia, and progressive movement impairment are frequently observed after early hypotonia (Li et al., 2022). The defining characteristic is self-injurious behavior (SIB), which usually starts between the ages of two and four. Biting of the lips, fingers, or tongue is one example of SIB (Negi et al., 2024). Convulsions, forced plantar grip, nystagmus, strabismus, and optic atrophy are further neurological symptoms that have been documented in recent cohorts (Fang et al., 2024; Park et al., 2023). MRI often reveals no major structural abnormality, supporting the notion that the disorder is primarily biochemical/neurochemical rather than destructive (Li et al., 2022).

Dopaminergic System in LNS

There is strong evidence that LNS significantly impairs dopaminergic function. A 2021 stem cell model of HPRT1 deletion midbrain dopaminergic progenitors, for instance, showed poor dopaminergic differentiation, decreased RHEB/mTORC1 signaling, and impaired glycolysis/oxidative phosphorylation (Bell et al., 2021). In a 2022 in vivo mouse model, HPRT loss caused aberrant dopaminergic circuit architecture by interfering with the migration, organization, and proliferation of midbrain dopamine (mDNA) neurons during embryogenesis (Witteveen et al., 2022). Additionally, PET imaging and cerebrospinal fluid studies show decreased levels of dopamine metabolites (HVA) and decreased uptake of ^18F-fluorodopa in the affected patients' basal ganglia (Bell et al., 2021; Li et al., 2022).

Dopamine/serotonin-mediated mechanisms

A growing body of research links LNS self-harm to striatal dopamine and serotonin (5-HT) problems. For instance, pharmacologic research suggests serotonin participation, while reduced dopamine levels suggest postsynaptic receptor super sensitivity (Reisz et al., 2023; Li et al., 2022). Early HPRT deficiency causes maladaptive changes in dopaminergic circuits, which increase susceptibility to compulsive self-harming behaviors, according to the developmental dopaminergic hypothesis (Bell et al., 2021).

Treatment of Lesch Nyhan Syndrome

Allopurinol

By reducing blood urate levels and preventing nephrolithiasis and gout, the first line of treatment uses xanthine oxidase inhibitors, mainly

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allopurinol, to address the overproduction of uric acid (Valechha et al., 2025; Fang et al., 2024). Allopurinol is useful in avoiding problems caused by uric acid; however, it has little effect on the neurological or behavioral symptoms of LNS. In addition to dietary control and hydration, febuxostat may be taken into consideration in circumstances where the patient is intolerant to allopurinol (Cheppalli & Andhi, 2023). It might be difficult to treat neurological disorders, including dystonia, spasticity, and involuntary movements, because pharmacological treatments don't always work. Although there is little and mostly anecdotal data to support their effectiveness, medications like baclofen, benzodiazepines, and injections of botulinum toxin are occasionally used to treat dystonia (Jinnah et al., 2024; Deng et al., 2023). Notably, levodopa and other dopaminergic drugs are ineffective and can exacerbate symptoms.

Deep Brain Stimulus

DBS of the globus pallidus internus (GPI) is a potential treatment for self-harming behavior and refractory motor symptoms. According to recent research, DBS can help some individuals with both dystonia and SIB, while results can vary and problems like hardware malfunction or infection can happen (Deng et al., 2023; Baird-Daniel et al., 2023). Behavioral therapy, protective gear (such as splints or customized mouthguards), and occasionally dental procedures like tooth extractions to avoid tissue damage are all used to manage self-harming behavior (Ierardo et al., 2020). Although there is a dearth of long-term data, pharmacological therapies like gabapentin or antipsychotics have been used off-label to reduce violent or obsessive behaviors. It may be necessary to use surgical or neuromodulation techniques when behavioral and pharmaceutical therapies don't work (Fig. 01).

An important part of managing LNS is providing supportive care. Regular physical and occupational treatment helps patients with movement issues, hypotonia, and spasticity. Since many patients have dysphagia and may need specialized feeding methods or equipment, speech and feeding therapy are crucial. Orthopedic procedures may be required for patients with contractures or abnormalities of the joints, and nutritional support is crucial to preventing failure to thrive.



Fig 01: Treatment of Lesch-Nyhan Syndrome

Frontier in Medical & Health Research

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Conclusion

Lesch-Nyhan Syndrome is a rare, X-linked recessive genetic disorder caused by mutations in the HPRT1 gene, which encodes the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT). This enzyme is crucial for the purine salvage pathway, and its deficiency leads to the accumulation of uric acid and various neurobehavioral abnormalities. Lesch-Nyhan syndrome is a devastating disorder with a wide spectrum of clinical severity, ranging from mild hyperuricemia to profound motor disability and severe self-injurious behavior. The disease is rooted in inborn metabolic dysfunction, but its consequences extend far beyond biochemistry, affecting neurological, behavioral, and physical development. Despite being discovered over 60 years ago, LNS remains incurable, and treatment is primarily symptomatic. New research into gene editing (CRISPR), stem cells, and deep brain stimulation shows promise but remains experimental. Early diagnosis, especially using genetic testing, is crucial for effective management and genetic counseling, particularly because carrier females may be asymptomatic but can transmit the disorder to male offspring. Although the metabolic complications can be effectively managed with uric acid-lowering therapies like allopurinol, the neurological and behavioral symptoms remain resistant to conventional treatment. Interventions such as deep brain stimulation (DBS), behavioral therapy, protective dental devices, and multidisciplinary supportive care offer some relief but are not curative. Recent advances in gene editing and cellular modeling offer hope for future disease-modifying therapies, though they are still in the experimental stage.

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