
**International Journal of Innovative Technologies in Social Science**

e-ISSN: 2544-9435

**Scholarly Publisher**
**RS Global Sp. z O.O.**
ISNI: 0000 0004 8495 2390

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| **ARTICLE TITLE** | LESCH – NYHAN SYNDROME (LNS) - THE REVIEW |
| **DOI** | https://doi.org/10.31435/ijitss.3(47).2025.3862 |
| **RECEIVED** | 29 July 2025 |
| **ACCEPTED** | 14 September 2025 |
| **PUBLISHED** | 30 September 2025 |
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# LESCH – NYHAN SYNDROME (LNS) - THE REVIEW

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**ABSTRACT**

Lesch-Nyhan syndrome (LNS) is a rare X-linked disorder caused by mutations in the HPRT1 gene, which encodes an important enzyme in the purine salvage pathway. Symptoms of LNS include dystonia, gout, intellectual disability, and self-harm. Although the disease was described in 1964, it remains unclear how abnormalities in hypoxanthine and guanine recycling can lead to such significant neurological deficits. Several studies have proposed different hypotheses regarding the etiology of the disease and various treatment options have been proposed, but none have led to a satisfactory explanation of the pathophysiology of the disease. New technologies such as sequencing, optogenetics, genome editing, and induced pluripotent stem cells may provide a unique opportunity to map the precise sequential pathways from genotype to disease phenotype.

**KEYWORDS**

Lesch – Nyhan Syndrome, HPRT1, Purine Salvage Pathway, Hyperuricemia

**CITATION**

Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik. (2025) Lesch–Nyhan Syndrome (LNS) – The Review. *International Journal of Innovative Technologies in Social Science*, 3(47). doi: 10.31435/ijitss.3(47).2025.3862



## Introduction

Lesch–Nyhan syndrome is a congenital disorder caused by a mutation in the HPRT1 gene located on the X chromosome at the Xq26-q27.2 locus and resulting deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT), which is involved in the purine salvage pathway.(Bell i in., 2021) It converts guanines and hypoxanthines into guanosine monophosphate and inosine monophosphate, respectively. Enzyme deficiency leads to an increase in guanine and hypoxanthine, which are ultimately converted to uric acid. HPRT deficiency causes a spectrum of clinical symptoms, the intensity of which depends on the severity of the enzyme deficiency. When the enzyme activity is less than 1.5%, a set of symptoms of significant severity is clinically presented.(Bell i in., 2016, 2021; Jathar i in., 2016) The abnormalities presented in the disease include: hyperuricemia, neurodevelopmental abnormalities, global developmental delay, involuntary movements and self-mutilating behavior. (Krajewski i in., 2024; Menozzi i in., 2019; Mohapatra & Sahoo, 2016; Park i in., 2023)In cases where HPRT activity is at a higher level (8% to 60%), we are dealing with Keeley-Seegmiller syndrome, which is accompanied only by symptoms related to hyperuricemia. Enzyme activity at a level of 1.5% to 2% results in hyperuricemia with neurological disability (dystonia, choreoathetosis, spasticity, intellectual disability).(Bell i in., 2016; Jathar i in., 2016)

## Clinical Symptoms

Symptoms of LNS are present at birth and gradually progress and intensify with age. Symptoms include neurological dysfunction, cognitive abnormalities, and hyperuricemia. Due to the location of the gene on the X chromosome, essentially all patients are males, who experience delayed growth and maturation disorders - testicular atrophy. Rare cases of co-occurrence of macrocytic anemia have been described - HGPRT deficiency causes the body to poorly utilize vitamin B12.(Basta & Pandya, 2025)

Increased uric acid levels resulting from the lack of HGPRT appear already in the first months of life and result in the occurrence of component symptoms: moderate mental retardation, gout, and weakened muscle control.(Bell i in., 2016)

The first neurological symptoms are reduced muscle tone (hypotonia) and developmental delay, which manifest between 3 and 6 months of age. Children affected by the disease sit up later, and most of them never crawl or walk.(Basta & Pandya, 2025; Fang i in., 2024; Petitgas i in., 2024) A commonly observed feature is the lack of speech. The predominant neurological symptoms in older children include: facial grimaces, involuntary movements of the arms and legs, and twisting of the limbs in an unnatural way (the picture may resemble the movements occurring in Huntington's chorea). The disease involves the extrapyramidal system, which results in abnormal involuntary muscle contractions, dystonia, choreoathetosis, and opisthotonus. In connection with the involvement of the pyramidal system, spasticity, hyperreflexia, and Babinski's sign occur.(Krajewski i in., 2024) The direct cause of the neurological abnormalities remains unknown. A problematic and difficult to prevent element of the symptoms of Lesch-Nyhan syndrome is self-mutilating behavior, which presents itself around the age of 2.(Fang i in., 2024) It manifests itself through biting the lips, skin, and fingers, leading to the formation of extensive and bleeding wounds.(Mohapatra & Sahoo, 2016; Park i in., 2023)

High levels of uric acid accompanying the disease can lead to the precipitation of monosodium urate crystals in the kidneys, joints, CNS, and other tissues. The consequences are gout attacks, accompanied by joint swelling, and urinary system abnormalities.

Urinary symptoms are among the first, occurring in infancy in the form of sand-like urate crystals observed in the diaper or hematuria resulting from their presence in the urinary tract.(Bell i in., 2016; Fang i in., 2024) The next stages are the precipitation of urate stones in the kidneys, ureters or bladder - which can

lead to obstruction at various levels of the urinary tract, numerous infections and kidney damage resulting from the presence of bacteria or obstruction. Despite the high production of uric acid, its elimination in the urine and precipitation is so rapid that its concentration in serum often remains within the normal range.(Petitgas i in., 2024) Stones can be the main feature of the disease, but it can sometimes take several months or even years to detect them.

**Treatment**

In the treatment of Lesch-Nyhan syndrome, the main role is played by the use of allopurinol. Thanks to its properties that allow it to lower the level of uric acid in the blood, it affects the symptoms caused by the accumulation of this substance, such as: arthritis, urinary tract symptoms. Unfortunately, neurological and cognitive symptoms and self-harm are not modified by the use of allopurinol.(Basta & Pandya, 2025; Menozzi i in., 2019; Park i in., 2023; Petitgas i in., 2024)

Kidney stones can be treated with surgical methods - lithotripsy is a method that involves breaking up stones using a laser or ultrasound waves. It is necessary to control the overproduction of uric acid in order to reduce the risk of urinary tract complications - nephropathy, kidney stones. Allopurinol is used to stop the conversion of oxypurines to uric acid and to prevent the formation of kidney stones and nephropathy.(Laróvere i in., 2021; Petitgas i in., 2024) It is recommended to select the dose in such a way as to restore the uric acid level to the correct concentration (<3 mg/dL).

The treatment of neurological symptoms in LNS is not defined by standards and there is no drug that would clearly lead to their limitation or remission.(Basta & Pandya, 2025; Krajewski i in., 2024; Menozzi i in., 2019) Symptomatic pharmacotherapy is used, selected individually depending on individual needs and response. The following are used: haloperidol, risperidone, phenobarbital, diazepam, levodopa.(Krajewski i in., 2024) Benzodiazepines and baclofen are used to reduce spasticity, allowing muscle relaxation and calming of the patient.

In order to reduce self-harm, physical methods are used, special protectors are proposed, placed in the elbow joints, aimed at limiting the flexion of the limb in the joint and making it difficult to bite the fingers and hands.(Jathar i in., 2016) Special spreaders are used, placed on the mouth and teeth, so as to prevent biting and biting the lips. In the past, in the most difficult cases presenting extensive self-harm, extraction of the front teeth was used as a preventive method.

No method of treating the neurobehavioral aspects of the disease is effective. Even in children treated with allopurinol from birth, behavioral and neurological problems develop, despite the fact that the level of uric acid in the serum was never too high. Auto-aggressive behaviors and other adverse behaviors can be treated by combining pharmacological, physical, and behavioral methods. Currently, there is no known method that would allow the disease to be cured, (Jathar i in., 2016; Krajewski i in., 2024) but interdisciplinary care for the patient allows survival into adulthood.

**Conclusions**

Lesch–Nyhan syndrome is an X-linked disease with an unclear pathophysiology. The key element is a significantly elevated uric acid level and subsequent deposition of crystals in the joints, urinary tract and tissues. The neurological and behavioral component is complex and does not improve with effective treatment to reduce uric acid levels. The drug used in each case is allopurinol, which allows for the elimination of excess uric acid. Other drugs are used symptomatically and do not eliminate the cause of the disease. An interdisciplinary approach focused on patient comfort and clinical response plays a key role in patient care.

**Disclosure**

**Author's Contribution:**

Conceptualization – Daria Madycka; Methodology - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Software - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Check - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Formal analysis - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Investigation - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Resources - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Data curation - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Writing (rough preparation) - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Writing (review and editing) - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Visualization - Daria Madycka, Weronika Skrzypek, Małgorzata Słaboń, Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik; Supervision - Daria Madycka; Project administration – Daria Madycka;

*All authors have read and agreed with the published version of the manuscript.*

**Funding Statement:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Conflict of Interest Statement:** The authors declare no conflict of interest.

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