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Symptomatic management and new therapeutic directions in Lesch-Nyhan syndrome (Review)

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Abstract. Lesch-Nyhan Syndrome (LNS) is a rare inborn error of metabolism caused by a deficiency in the hypoxanthine-guanine phosphoribosyl transferase enzyme. The condition manifests through a range of symptoms, including dystonia, gout, megaloblastic anemia, hyperuricemia, intellectual disability and self-mutilation behaviors. As a genetic disorder, LNS lacks a definitive cure, and current treatments are primarily symptomatic. Due to the rarity of LNS and an incomplete understanding of its complex pathophysiology, to date, to the best of our knowledge, no therapies exist that can fully address the root cause of the disease. The present review aimed to provide a comprehensive overview of the latest advancements in understanding the pathophysiology of LNS to promote the further exploration of emerging therapeutic approaches that exhibit potential for use in the management or mitigation of LNS symptoms.

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Abbreviations: LNS, Lesch Nyhan syndrome; HGPRT, hypoxanthine guanine phosphoribosyl transferase; LNVs, Lesch-Nyhan variants; EPAC, exchange protein activated by cAMP; iPSCs, induced pluripotent stem cells; WMV, white matter volume; GMV, grey matter volume; GMP, guanosine monophosphate; IMP, inosine monophosphate; HND, HGPRT-related neurologic dysfunction; HRH, HGPRT-related hyperuricemia; SIB, self-injurious behavior; AADC, aromatic-L-amino acid decarboxylase; CNS, central nervous system; HAP1 cells, human near-haploid cells; DBS, deep brain stimulation; CBEs, cytosine base editors; EPO, erythropoietin; BTX-A, botulinum toxin A; p-ERK, phosphorylated ERK; CREB, cAMP response element-binding protein; SAMe, S-adenosyl methionine; GP, globus pallidus; pegRNA, prime editing guide RNA; PEs, prime editors

Key words: Lesch-Nyhan syndrome, self-mutilation, pathophysiology, therapeutics

Contents

1. Introduction

Lesch Nyhan syndrome (LNS) is a rare X-linked recessive disorder that affects between 1 case per 235,000 births and 1 case per 380,000 live births (1). It is an inborn error of metabolism and is associated with a deficiency of the hypoxanthine guanine phosphoribosyl transferase (HGPRT) enzyme. HGPRT is a purine salvage enzyme that converts the free purine bases guanine and hypoxanthine into their utilizable forms, guanosine monophosphate (GMP) and inosine monophosphate (IMP), respectively. Due to the X-linked genetic etiology, mostly males develop LNS, with females exhibiting some mild symptoms (2). However, females can also develop the disease if the chromosome containing the wild-type allele for HGPRT undergoes random X inactivation or lyonization, and the chromosome with the mutant/defective HGPRT allele is expressed (3). A deficiency in HGPRT is linked to the following: i) The overproduction of uric acid, resulting in gouty arthritis and kidney and bladder stones. ii) Hematological symptoms, such as megaloblastic anemia (4). iii) Neuropathology, causing mental retardation, spastic cerebral palsy, choreoathetosis and self-injurious behavior (SIB). SIB includes lip, finger and tongue biting, and banging head/limbs (5). Patients have been reported to lose parts or all of their tongue, fingers and toes (6). iv) Abnormal involuntary muscle movements, such as dystonia, choreoathetosis, opisthotonos, and ballismus (7,8). Treatment is symptomatic and supportive, and affected individuals do not survive the first or second decade of life due to renal failure.

LNS manifests itself severely and has a varying level of effects on individuals suffering from it due to either the complete [Lesch-Nyhan disease (LND)] or partial loss of HGPRT activity [Lesch-Nyhan variants (LNVs)]. These two terms distinguish spectrum of severity associated with HGPRT deficiency. However, the severity of neurological and

behavioral symptoms may vary depending on the amount of residual HGPRT activity. One of the most severe neurological impairments is not being able to walk (9,10). LNV is divided into two main types of clinical phenotypes: i) HGPRT-related neurologic dysfunction (HND); and ii) HGPRT-related hyperuricemia (HRH), also known as Kelley-Seegmiller syndrome, associated with the marked overproduction of uric acid, resulting in hyperuricemia, nephrolithiasis and gout (11). LNV is a milder form of the disease characterized by less severe neurological and motor impairments and does not include self-injurious behavior.

LNS presents various types of clinical signs, such as decreased gray and white matter in the brain, hypercoagulability and intellectual deficit (12,13). Imaging techniques, such as diffusion tensor imaging reveal the subtle loss of white matter integrity, particularly in the corpus callosum, corona radiata, cingulum, internal capsule and superior longitudinal fasciculus in the brains of patients with LND compared to controls (14). By contrast, voxel-based morphometric analyses determine the gray or white matter volume of the LND. The gray matter volume (GMV) and white matter volume (WMV) are significantly reduced in the brains of patients with LND compared to healthy controls and those with LNVs. For instance, a 20% reduction in the total intracranial volume has been observed in the brains of patients with LND compared to a 14% reduction in those with LNVs. Furthermore, reductions in WMV (26.2%) are more prominent than those in GMV (17%) in the brains of patients with LND (15). The loss of gray matter has been shown to be associated with specific sites, such as the caudate, thalamus and anterior putamen. The putamen and caudate nucleus together form the corpus striatum, which is part of the forebrain. However, neurodegeneration was not detected in these studies, despite the loss of WMV and GMV (14,15).

During the first few months of life, affected children appear normal. The majority of individuals seek medical care at a young age, typically before 4 years of age. The main causes of mortality in these patients are aspiration pneumonitis and kidney failure (16). Given that LNS is a genetic condition, there is no known treatment for it. Treatment with xanthine oxidase inhibitors is generally effective at reducing the elevated levels of uric acid; however, there is no specific treatment available for other symptoms. Due to its low frequency and the incomplete understanding of the pathophysiological mechanisms, treatments are usually administered to reduce symptoms. The present review discusses the genomics and advancements in the pathophysiological mechanisms of the disease, including promising therapeutics and associated challenges in the treatment of patients with LNS. While several review articles on LNS have been published to date (1,17-19), the present review distinguishes itself by integrating the latest research up to November 30, 2024, with a focus on genomic advancements, detailed neuroimaging analysis, pathophysiology and promising therapeutic interventions. Additionally, the present review critically evaluates the challenges encountered in the management of LNS, providing a comprehensive synthesis of recent findings and their clinical relevance. An extensive search of the literature was performed using three online databases: PubMed, Embase and Web of Science. The search was carried out from the beginning of the databases up until November 30, 2024. A combination of the following key words was used: LNS, LND, SIB, mutations in LNS, therapeutic approaches in LNS, therapeutic drugs, inhibitors, drugs, neurological disorders and clinical trials, case studies of LNS, case reports of LNS. The inclusion criteria required studies on participants with confirmed LNS. Studies not containing sufficient data for analysis, commentaries, or editorials without primary data, animal or *in vitro* studies that lacked direct clinical relevance, studies published in languages other than English, and duplicate publications or reports with overlapping data were excluded.

2. Genomics of LNS

Human *hgprt1* is a housekeeping gene. It is present on chromosome Xq26.2-q26.3, and codes for HGPRT. HGPRT, through its transferase activity, carries out the conversion of hypoxanthine and guanine to IMP and GMP, respectively by transferring 5-phosphoribosyl group from 5-phosphoribosyl 1-pyrophosphate (20). The highest expression of gene has been observed in the testes followed by the brain tissue. However, the lowest expression has been observed in the salivary glands, followed by the pancreas. The salivary gland has only one functional mRNA transcript (21). This gene consists of eight introns and nine exons. These exons encode 218 amino acids with a protein size of 24.5 kDa. The majority of mutations are observed within the intronic and exonic regions of Xq26-q27, which manifests itself as reduced activity of hypoxanthine guanine phosphoribosyl transferase, leading to gout and other characteristic abnormalities (2). Depending on the mutation, the enzyme exhibits no or residual enzymatic activity (11,22). Different mutations in *hgprt1* lead to a differential expression and produce different variants designated as LNVs. Notably, ~68% of the mutations in the LND group are deletion, insertion, nonsense and splicing mutations, leading to undetectable enzyme function. In the HND and HRH types of LNVs, the majority of mutations are missense mutations (88%). Therefore, LNVs demonstrated residual HGPRT activity (22). Residual activity is associated with the severity of symptoms, particularly the extent of neurological disturbances (22). Disease severity is associated with changes in the purine metabolism rate. Patients with <2% HGPRT activity demonstrate self-mutilative behaviors, involuntary movements, intellectual deficits, and hyperuricemia (23). On the other hand, the partial deficiency of HGPRT activity (>2%) causes hyperuricemia with only mild neuropsychiatric symptoms (24). Of note, a previous study demonstrated there was no significant difference in the levels of uric acid in the serum of patients with HRD, HRH and LND, ruling out the possibility of uric acid involvement in developing a neurobehavioral phenotype in LNS (25). By contrast, mutations are not always deleterious and may occasionally improve enzyme activity. However, activity never returns to normal levels (26).

Currently, the etiology of LNS, is caused by >2,000 identified genetic alterations in the *hgprt* gene (http://www.lesch-nyhan.org/en/research/mutations-database/) (21,27). Mutations are distributed throughout the gene, and no hotspots or clusters have been identified (22). This indicates that multiple mutations in *hgprt* can cause unique LND. Of note, >600 pathogenic variations linked to LND have been

identified to date (28). Several novel mutations have also been identified over the past 5 years (4,29,30). As per the literature, only 15 cases in females have been shown to be affected by LNS (23,31-39). These mutations include: i) Nonsense mutations (p.Arg170*, C151T, and p.Tyr153*); ii) missense mutations (p.Glu14Lys and p.Tyr72Cys); iii) splice site mutations (c.609+4A>G and IVS8+4A>G; iv) translocation severe [46,XX,t(X:2)(q26:p25)]; v) one microdeletion of HGPRT; and vi) a frameshift mutation (c.539delG). The possible reason for LNS in females may be the non-random inactivation of the normal allele; therefore, females have only a mutated copy of the HGPRT allele. For example, in a previous study, when genomic DNA from whole blood samples was amplified without *Hha*I digestion, two polymorphic alleles at the AR locus were detected. However, following the *Hha*I digestion of blood samples from the affected girl and her mother, only the AR1 allele was amplified, suggesting the presence of non-random X-inactivation in the patient (38).

3. Pathophysiology of LNS

Mutations in the HGPRT gene cause enzyme dysfunction, leading to LND, characterized by gout, self-injurious behavior and neurological symptoms. HGPRT deficiency disrupts the purine salvage pathway, causing hypoxanthine accumulation, which is oxidized to urate, leading to gout, renal dysfunction, and oxidative stress (40). The molecular mechanisms behind the neurological and neuropsychiatric symptoms remain unclear, impeding treatment. The multi-faceted effects of HGPRT mutations on mitochondrial function, purine nucleotide metabolism and signaling pathways remain underexplored. Emerging studies have shown that disruptions in the function of HGPRT alter exchange protein activated by cAMP (EPAC)/RAP1 signaling, AMP-activated protein kinase activation due to PARP accumulation, folic acid levels, dopaminergic function, cell motility and cytoskeletal dynamics, all of which contribute to the neurodevelopmental and motor deficits observed in LNS (41-43). Experimental models confirm neurological, renal and metabolic defects, highlighting potential therapeutics, such as allopurinol, dopamine receptor agonists and gene editing to manage or treat HGPRT-related conditions (44). While attempts have been made to link HGPRT deficiency to these symptoms, the exact association of HGPRT with LND is not yet fully understood. It is also not clear how neurons respond to the levels of HGPRT; hence, treatment is greatly impeded due to the lack of knowledge about the mechanisms of HGPRT.

Mechanisms of HGPRT-associated anemia. Macrocytic anemia is another typical feature of LND and LNV, which is not widely recognized due to insufficient documentation of its occurrence, intensity, or medical importance in the literature (45,46). The prevalence of macrocytic erythrocytes in subjects with LND and LNV with or without anemia is relatively high. Macrocytic erythrocytes have been shown to occur in 81-92% of subjects with LND and LNV. This high prevalence underscores the significance of macrocytic erythrocytes as a common aspect of the clinical phenotype in individuals with LND and its variants (12).

Plasma hypoxanthine levels are a sensitive parameter for hypoxia in fetuses and newborns. Thus, the hypoxanthine level can be used as a potent indicator of hypoxia. Hypoxia increases purine nucleotide breakdown, generating high levels of hypoxanthine as a by-product. In patients with LND, the combination of hypoxia-induced hypoxanthine generation and HGPRT deficiency exacerbates the accumulation of hypoxanthine, contributing biochemical, renal and neurological manifestations (2,47,48). This highlights the vulnerability of patients with LND to any additional stressors, such as hypoxia, that may further overload the purine metabolism pathway. *In vivo*, hypoxanthine is formed by the dephosphorylation and deamination of ATP and is a hallmark of hypoxia-induced mitochondrial dysfunction. First, oxygen is required for the proper functioning of the electron transport chain and oxidative phosphorylation in the mitochondria, which ultimately produces ATP. Under low oxygen conditions, these processes are disrupted, resulting in decreased ATP production and adenosine monophosphate (AMP) accumulation. To meet these energy requirements, AMP is degraded to compensate for the loss of ATP. The increased production and degradation of AMP leads to hypoxanthine production (Fig. 1). This is the mechanism through which cells adapt to low oxygen concentrations by altering their metabolic pathways. In addition, during hypoxia, xanthine oxidase is inhibited, leading to the accumulation of hypoxanthine (49,50). The exposure of red blood cells (RBCs) to oxidative stress, whether *in vivo* or *ex vivo*, enhances purine deamination through AMP deaminase 3. This process leads to the increased accumulation of hypoxanthine, a deaminated purine. This increase in hypoxanthine levels is accompanied by changes in the morphology of RBCs, followed by increased destruction outside the blood vessels via splenic sequestration and erythrophagocytosis (51). Additionally, low oxygen levels trigger erythropoietin (EPO) gene expression, which codes for the glycoprotein hormone erythropoietin. The kidneys are the main organ in an adult organism that produces EPO (46). The glycoprotein hormone EPO increases the ability of the body to carry oxygen by encouraging the development and differentiation of erythroid precursor cells in the bone marrow, leading to an increase in red blood cell mass and macrocytic anemia.

A previous study demonstrated that RBCs from patients with LNS exhibit an accumulation of glycolytic intermediates upstream of pyruvate kinase along with elevated levels of unsaturated fatty acids and long-chain acylcarnitines. Additionally, there is an increase in highly unsaturated phosphatidylcholines in the RBCs of these patients, while free choline levels are decreased. Furthermore, intracellular concentrations of iron, zinc, selenium and potassium are also reduced in the RBCs of patients with LNS (2). Global proteomic analyses have documented alterations in RBC membrane proteins, hemoglobin, redox homeostasis proteins and the enrichment of coagulation proteins. These changes are accompanied by increased protein glutamine deamidation and methylation in both children with LNS and their carrier mothers. Allopurinol treatment partially reverses these phenotypes. However, these changes have been specifically noted in the context of the HGPRT gene mutation c.485 G>A. Ser162Asn (2). These findings suggest that complementary treatments, in addition to current regimens, such as allopurinol, could involve the supplementation of substrates to

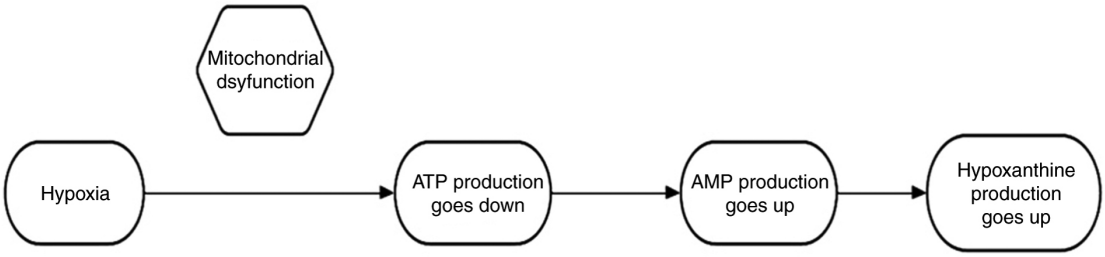

Figure 1. Hypoxanthine as a biomarker for hypoxia.

activate compensatory regulatory pathways (2). Additionally, the recycling of hypoxanthine by the X-linked HGPRT plays a crucial role in maintaining IMP/GMP homeostasis in RBCs. In patients with LNS, genetic mutations in this enzyme result in various clinical symptoms, including macrocytic anemia (12).

Mechanisms of HGPRT-associated neurobehavioral problems. HGPRT deficiency also affects behavioral symptoms, which are a consequence of disrupted dopamine pathways in the basal ganglia (52). Previous research was conducted to elucidate the dysregulation in the development of dopamine neurons in MN9D derived HGPRT-ve (HGPRT-deficient) cell lines (52,53). Two mechanisms were proposed based on the results of that study: i) Microarray analysis of these cell lines revealed the diminished expression of tyrosine hydroxylase. This result is in line with previous experiments conducted to demonstrate the dysregulation of biochemical markers related to the dopamine phenotype (52). ii) Another finding was the overexpression of engrailed genes *En 1* and *En2,* which are transcription factors that play vital roles in neural development, that is, the development and survival of dopamine neurons. The results revealed that *En2* was expressed in all fibroblasts and in higher amounts in patients with neurobehavioral problems, suggesting an inverse relationship between HGPRT and *En*. However, the mechanism by which HGPRT levels regulate the expression of *En* genes is yet to be determined (53).

Similarly, HGPRT deficiency has also been shown to exhibit a deregulatory effect on guanine metabolism, and hence, it affects G protein-coupled receptor (GPCR) expression. For instance, altered and structurally defective expression of P2Y1 (GPCR) is associated with aberrantly phosphorylated ERK (p-ERK) and cAMP response element-binding protein (CREB) signaling (54). Notably, p-ERK can be transported into the nucleus, where it activates various transcription factors, such as CREB. CREB is crucial for the transcription of numerous neuronal genes, and is essential for long-term synaptic plasticity. Therefore, defects in these genes may affect neuronal development. Compared to LNV, patients with LND exhibit greater reductions in fractional anisotropy across the brain and specific disruptions in the corpus callosum, corona radiata, cingulum, internal capsule and superior longitudinal fasciculus. These deficits in white matter organization are associated with more severe dystonia and cognitive impairments, highlighting the need for the further exploration of the role of white matter in the pathogenesis of LND (14). Emerging studies emphasize that HGPRT deficiency affects neurodevelopment and neurocognitive function through metabolic and cellular disruptions. For example, alterations in white matter integrity, reduced neuronal connectivity and neurobehavioral symptoms have been linked to changes in neurexin expression, genes critical for synaptic function that are associated with autism, schizophrenia, and Alzheimer's and Parkinson's disease (55). NAV3, another identified gene, has been implicated in neurodevelopmental disorders and neuromuscular responses, further suggesting a role in LND-associated neuronal morphogenesis (56). Additionally, hypoxia-induced increases in hypoxanthine levels, a characteristic metabolic disruption in LND, underline the pathophysiological burden on both the central nervous system and peripheral processes. This highlights the interplay between metabolic imbalances and neurobehavioral outcomes in HGPRT deficiency. Stratification studies from analogous conditions, such as traumatic brain injury, suggest that white matter disorganization may serve as a prognostic biomarker for neurocognitive trajectories and may provide a framework for understanding HGPRT-associated symptoms (57). These findings collectively underscore the critical need to elucidate the molecular and structural underpinnings of HGPRT-associated neurobehavioral deficits, aiming to identify targeted therapeutic interventions and improve the quality of life of affected individuals. A previous study revealed that several microRNAs (miRNAs/miRs) from the miR-17 family cluster, along with genes encoding guanine nucleotide exchange factors, are dysregulated in HGPRT deficiency (41). Notably, the EPAC displays a reduced expression in HGPRT-deficient human neuron-like cell lines and fibroblast cells from patients with LNS. Similar alterations have been observed in the cortex, striatum and midbrain of HGPRT knockout mice (41). These dysregulations lead to the impaired activation of the small GTPase RAP1, which is critical for cytoskeletal dynamics. Consequently, HGPRT-deficient cells exhibit an altered motility compared to controls. HGPRT deficiency also results in the dysregulation of miR-181a (58). The expression of miR-181a is elevated in HGPRT-deficient human dopaminergic SH-SY5Y neuroblastoma cells, which in turn leads to the aberrant expression of target genes involved in mammalian central nervous system (CNS) development (59). Utilizing miRNA-based target predictions, researchers have identified critical signaling pathways for potential therapeutic targeting in LNS. A hypothetical model further proposes that HGPRT mRNA transcripts function as competitive endogenous RNAs, engaging in complex regulatory crosstalk with key neural transcripts and miRNAs, potentially amplifying the gene's pleiotropic effects on diverse pathways (60). To further investigate these mechanisms, fibroblasts derived from patients with LNS were reprogrammed into induced pluripotent stem cells (iPSCs) using a combined miRNA/mRNA

reprogramming approach (61). This innovative methodology facilitated the development of LNS-specific iPSC lines for in-depth mechanistic and therapeutic research, providing a valuable model system for dissecting the molecular basis of this rare metabolic disorder and guiding the identification of novel biological targets.

Effect of HGPRT deficiency on mitochondrial function. Another study was conducted to further elucidate the effects of HGPRT on mitochondrial energy metabolism in the brain (24). The researchers used a CRISPR mouse as their model organism, which carried the same Hgprt1^del8Val mutation as found in humans for LN. This mutation causes the homodimerization of HGPRT, thereby reducing its activity. These findings indicate that there is an inhibitory effect of HGPRT deficiency on complex I, that is, NADH:ubiquinone oxidoreductase. As a result, the rate of consumption of NADH is suppressed, which ultimately results in decrease in mitochondrial membrane potential and increased mitochondrial reactive oxygen species (ROS) production. The increase in mitochondrial ROS production may be due to increased levels of xanthine, leading to the production of superoxide anions by oxidase (62,63). This diminished membrane potential leads to decreased ATP production. The low consumption of NADH by complex I results in NADH accumulation. To compensate for lower levels of ATP, cells acquire glycolysis (anaerobic metabolism) to fulfil their energy requirements, particularly when mitochondrial respiration is compromised owing to the inhibition of complex I. The HGPRT deficiency inhibits complex I-dependent mitochondrial respiration, leading to elevated mitochondrial NADH levels, a reduction in mitochondrial membrane potential, and an increased production rate of ROS in both the mitochondria and cytosol. Despite the heightened ROS production, there is no evidence of oxidative stress, as endogenous glutathione levels remain unaffected. This suggests that the disruption of mitochondrial energy metabolism, rather than oxidative stress, may act as a trigger for the brain pathology characteristic of LNS (24).

Further research using HGPRT-deficient rat B103 neuroblastoma models has identified a significant reduction in adenylate cyclase 2 expression, implying a potentially critical role of adenylate cyclase 2 in LNS-associated neurobehavioral abnormalities (64). However, validation in more advanced models, such as *in vivo* systems, is necessary to better elucidate the association between adenylate cyclase 2 and the pathogenesis of LNS (65). These findings highlight the critical link between HGPRT deficiency, mitochondrial dysfunction, and the downstream neurological impacts of LNS.

4. Current drugs and promising therapeutics

To the best of our knowledge, there is no curative treatment for LNS due to the lack of knowledge about the mechanisms associated with SIB, low intellect, depression and neurological dysfunction. Treatments are available on the basis of symptoms. However, reduction in one symptom will not always necessarily also lead to the suppression of another symptom. For example, treatments used to reduce uric acid will not reduce SIB as uric acid levels are not associated with the neurological manifestations of LNS.

Oral appliances. One strategy for the prevention of SIB is through tooth removal. However, this method is not ethical and is not permitted for use by the majority of parents. Personalized/customized intraoral devices and lip bumpers/lip guards are alternative options for the removal of teeth and are used to prevent oral and peri-oral trauma following their application (66,67).

Botulinum toxin A (BTX-A). Botulinum is a toxic compound produced by Clostridium botulinum and other related species, such as *Clostridium butyrricum, Clostridium barati, and Clostridium argentinensis*. Botulinum toxin works by blocking the release of the neurotransmitter acetylcholine, which activates muscle cells and helps them to contract. Thus, when acetylcholine is not released, muscles are in a relaxed state. This toxin is potentially toxic to nerve cells and thus causes paralysis; however, it can be used in optimal or controlled amounts (Fig. 2). BTX-A is also used to reduce the need for more invasive interventions, such as tooth extraction in patients with LNS. To date, there are only a few reported cases of patients with LNS treated with BTX-A; however, these cases vary in terms of dose, site and duration of the injection (Table I) (68,69).

Levodopa. Patients with LNS have low levels of dopamine in the basal ganglia due to the reduced activity of tyrosine hydroxylase, which is the rate-limiting enzyme in dopamine synthesis (70,71). Low levels of dopamine are associated with uncontrolled body movements. Of note, an ~50-63% reduction in the binding of the WIN-35,428 ligand to dopamine transporter was shown in the caudate region and a 64-75% reduction in the putamen region in patients with LNS (72). Therefore, to compensate for the loss of dopamine, levodopa (L-DOPA) is administered to treat movement disorders and SIB. Levodopa is a dopamine precursor, which is metabolized to dopamine in the periphery and in the CNS. Aromatic-L-amino acid decarboxylase (AADC) converts levodopa to dopamine. In contrast to dopamine, levodopa can cross the blood-brain barrier. Therefore, levodopa is prescribed over the direct injection of dopamine. However, the bioavailability of levodopa is low in the CNS. To overcome this issue, levodopa is administered in combination with carbidopa. Carbidopa (L-alpha-methyldopa hydrazine inhibits AADC by binding irreversibly to pyridoxal 5'phosphate, thereby blocking the conversion of levodopa to dopamine in the periphery. However, it does not block conversion in the CNS. Therefore, carbidopa increases the bioavailability of dopamine in the CNS. It also reduces the side-effects associated with the use of levodopa, such as nausea, vomiting and diarrhea. However, the results have been inconsistent and not encouraging (Table II) (73).

Due to these unanticipated complications, which worsen the condition of patients, none of the patients have completed the planned titration phase. Levodopa has no effects on the behavioral aspects, but triggers more adverse motor movements (73-75). These results suggest that the use of levodopa and carbidopa is not advantageous for reducing the symptoms of patients with LNS. It is possible that the mechanism in LND is different than from in DOPA-responsive dystonia, and the responses to medications may not be similar. Therefore, it may be interesting to determine the mechanisms underlying the

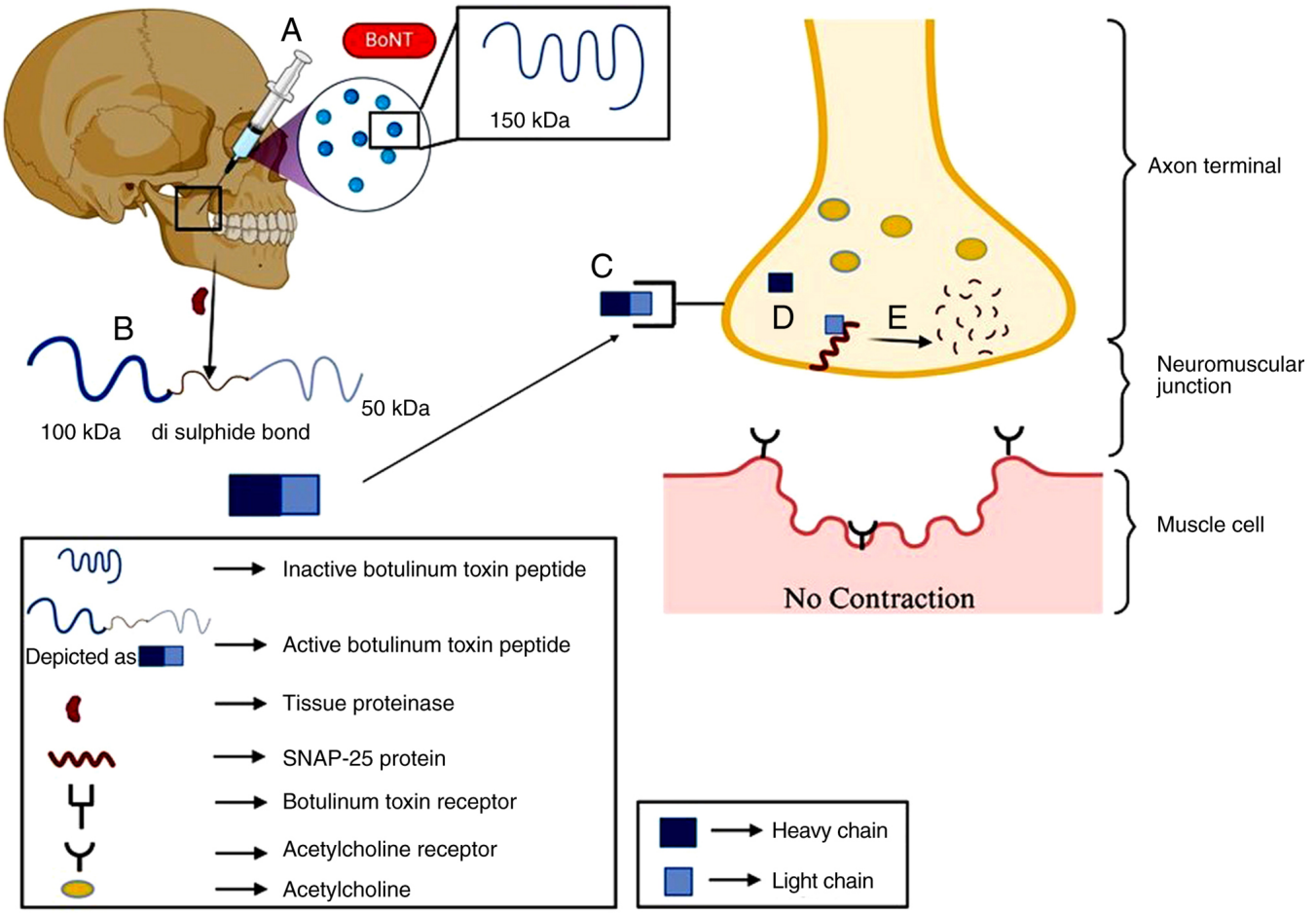

Figure 2. (A) Botulinum toxin (in inactive form) is injected into the masseter muscles where it is (B) converted into its active form, via the action of tissue proteinase (C) the activated botulinum toxin then binds to its receptor present on the axonal terminal and is brought into the cell (D) where it breaks off into heavy and light chains (E) the light chain then binds and mediates the cleavage of SNAP-25 protein, thereby ceasing the release of excitatory neurotransmitter acetylcholine.

lack of response to these two drugs in patients with LNS. These types of studies require replica HGPRT-deficient models that can help in determining the cause of drug failure. In addition, instead of combinion therapy, monotherapies of levodopa and carbidopa should be attempted in LNS models. It is essential to consider the fact that carbidopa inhibits AADC activity and, therefore, blocks the conversion of levodopa to dopamine.

S-adenosyl methionine (SAMe). SAMe is broken down to yield an adenosyl moiety, which is then converted into AMP (76). This AMP can be converted into either ATP or GTP in the brain, thereby replenishing the nucleotide pool in patients with LND that is otherwise depleted, thereby improving their condition. SAMe supplementation may help reduce the extrapyramidal symptoms associated with dopamine hypersensitivity by boosting the synthesis of GTP, which is crucial for dopamine production, and by enhancing the function of catechol-*O*-methyltransferase, an enzyme that plays a role in the inactivation of dopamine. Moreover, SAMe is readily taken up into the bloodstream and can cross the blood brain barrier, thereby making purine nucleotides available in the brain. Thus, it can also be used to treat other mental health disorders related to nucleotide depletion. The results of the use if SAMe have been encouraging in patients with LNS (Table III) (7,77,78). From these cases, it is evident that SAMe tends to be more effective in younger patients with LND. However, further research in the context of age-related responses to SAMe is required.

Allopurinol. Allopurinol is converted to its active metabolite, oxypurinol, which inhibits xanthine oxidase. Xanthine oxidase is the enzyme that converts hypoxanthine to xanthine and further to uric acid. Therefore, it first stops the production of uric acid and then increases the concentration of both hypoxanthine and xanthine in serum and urine (Fig. 3). The renal clearance of hypoxanthine and xanthine is very rapid compared to that of uric acid, and its plasma concentration is only partly elevated (79). The half-life of allopurinol is ~1-3 h and that of oxypurinol is 12-30 h. When Allopurinol is not used, these oxypurines are secreted through the urine in the form of uric acid. However, when allopurinol is administered, the urinary output is composed of hypoxanthine, xanthine and some amounts of uric acid, thereby reducing the risk of crystalluria, a condition characterized by the presence of uric acid crystals in urine, nephrolithiasis, nephrocalcinosis, and sometimes, acute or chronic kidney impairment (80). These oxypurines are easily cleared by kidneys. Advanced stages of gout are characterized by the formation of tophi, which

Table I. Case studies on the use of botulinum toxin A in LNS in the literature.

Age and sex of the patient(s)	Symptom	Other treatments given prior to BTX-A	Dose of BTX-A	Outcome	(Refs.)
10-year-old male (age at diagnosis, 8 years)	Cerebral palsy, developmental delay and had cognitive impairments, SIB, spasticity, dystonic movements, and hyperkinetic dyskinesia	Allopurinol	20 units of BTX-A every 12 weeks for three series of visits were given to masseter muscles.	Overall positive. i) Sores on hands, lips and tongue healed completely; ii) improved speech articulation, weight and height; iii) reduced SIB, aggression and medications.	(68)
30-year-old male (age at diagnosis, 12 years)	Dystonic posturing, cognitive disturbances, SIB	Allopurinol, baclofen, clonazepam, quetiapine, and L-carnitine.	Zygomatic muscles: 12.5 IU each; lower part of the lip orbicularis muscle in 6 injection sites: 2.5 IU each; levator labii inferioris in three injection sites: 5 IU each.	Overall positive. i) The muscles became hypotonic and weak; ii) and biting ceased with progressive healing of the wounds. He is currently on the waiting list for DBS.	(97)
12-year-old male	Generalized dystonia, choreoathetosis, opisthotonus, and spasticity and SIB	Four-point restraints to prevent self-harm.	Serial botulinum toxin type A injections (incobotulinum toxin A (Xeomin) and onabotulinum toxin A (Botox) to triceps, biceps, gastrocnemius, hamstring, quadriceps, and extensor hallucis longus at a dose 10 mg/kg every 8-12 weeks.	Overall positive. i) Dystonia and opisthotonus were significantly improved; ii) marked decrease in self-injurious behaviors.	(98)
13-year-old male	SIB, spasticity, dystonia and anxiety	Carbidopa-levodopa, fluoxetine, gabapentin, clonazepam, olanzapine, and oral baclofen.	BTX-A was administered to bilateral masseters at the dose of 50 units on each side with the help of ultra sound and electric stimulation for every 4-6 months.	i) Increased speech volume and a reduction in articulation errors, ii) decreased SIB behavior, and increased durations of effects.	(99)
6 patients with LND Age, 4, 4.5, 6.6, 7.9, 13.9, and 32.3 years	SIB	No information available.	Botulinum was given in combination with Dysport, with the highest total dosage of Dysport being 37.5 units/kg mean, whereas the highest total dose of Botox was 21.3 units/kg mean. The average number of shots given to the patients was 20, with a range of 3 to 29. Site of injection: masticatory muscles (masseter and temporalis), biceps brachii, and other muscles. Duration of injection: 1.5 to 7.1 years.	95% success rates. A total of 119 injections were administered, out of which 113 were partially or completely effective in ceasing the biting tendencies of patients, and only 3 produced some adverse effects.	(69)

Table II. Case studies of levodopa A in LNS identified in the literature.

Patient	Age, years	Mutation	Symptoms	Treatment administered	Dose of L-DOPA	Improvement in SIB	(Refs.)
1	27	428-432del TGCAG, insAGCAAA	Dystonia, chorea, ballism, hypotonia, opisthotonus, hyperreflexia, lip and finger biting	Allopurinol and chlorothiazide medications	L-DOPA administered in combination with carbidopa at a 4:1 ratio. L-DOPA/carbidopa for 4 weeks, and the maximum concentration was 600/150 mg daily	No	(73)
2	12	IVS7+5G>A	Dystonia, rigidity, spasticity, hyperlexia, head banging and biting	Allopurinol, diazepam, omeprazole, fluticasone, mometasone, cetirizine, levalbuterol	L-DOPA/carbidopa for just 1 day, and the maximum concentration he was given was 50/12.5	Discontinued the treatment	(73)
3	10	IVS7+5G>A	Dystonia, hypotonia, and biting of fingers and arms	Allopurinol and diazepam	L-DOPA/carbidopa 50/12.5 mg	Discontinued after first dose due to hyperactivity	(73)
4	3	10delC	Hypotonia, dystonia, thrashing and mouth biting	Allopurinol, gabapentin and lorazepam	L-DOPA/carbidopa for 4 weeks and had the maximum concentration of 150/37.5 mg	Agitated movements but levodopa treatment had positive effects on his behavioral aspects. The boy was in A good mood and did not bite his mouth very often and did not require any restraints	(73)

Table III. Case studies of SAMe in LNS identified in the literature.

Age and sex of the patient(s)	Symptoms	Mutation	Other treatments	Dose	Outcome	(Refs.)
43 years, male	SIB, dystonic paralysis, seizures, suspected but ill-defined pain, and renal stones.	Not available	Fentanyl 25 μg (by skin patch, every three days)	800 mg twice daily (on an empty stomach)	Positive. i) Delf-abusive behaviors disappearrf in 1.5 years; ii) improved liver function; iii) mood rating improved from 36 to 96% in 3 years.	(77)
15 years, male (age at diagnosis, 3.6 years)	SIB, spasticity and dystonia, severe hyperuricemia and hyperuricosuria	Deletion of exons 1,2 and 3	Allopurinol, diazepam and carbamazepine	22 mg/kg/day	Positive.	(100)
7 years, girl (age at diagnosis, 6 months) and 3 male cousins (ages: 13, 3.6 years, and 4 days)	Girl: SIB, dystonia, medullary nephrocalcinosis Males: Dystonia, limb hypertonicity, severe hyperuricemia and hyperuricosuria	Girl: Skewed x-inactivation of >95% of wild-type HPRT1 alleles in peripheral blood cells Males: HPRT1 intronic splice site mutation c.610-1G>A	Girl: Allopurinol (18 mg/kg/day) and oral baclofen (2.5 mg bd) commenced at age 10 months and 15 months, respectively Males: Oral baclofen (1 mg tds), allopurinol	Girl: 33 mg/kg/day Males: ~21 mg/kg/day or 26 mg/kg/day	Self-abusive behaviors and aggression were resolved and it also helped with dystonia.	(100)
14 patients (age: 11-49 years)	Hyperuricemia, SIB, anxiety, disturbed sleep pattern. recurrent uncontrolled bodily movements	Not reported	Allopurinol	Not available	SAMe treatment worked only for 4 out of 14 patients. P#1 speech and anxiety resolved, in P#12 and P#14 SIB resolved and P#13 sleep pattern improved. All others had to drop out of the trial due to SIB, anxiety, sleep pattern, recurrent uncontrolled bodily movements. Possible reasons for failure of this conduct could be difference in individual's age, ethnicity, drug metabolism and tolerance, severity of genetic mutation, environmental factors. Also, these patients were previously on other drugs too which weren't stopped when they received SAMe. This could have interfered with SAMe action.	(78)

Table III. Continued.

Age and sex of the patient(s)	Symptoms	Mutation	Other treatments	Dose	Outcome	(Refs.)
6 months, male	Motor development delay, poor head control, generalized muscle contractions, SIB, marked loss of muscle tone hyperuricemia (10.3 mg/dl), and an increased urinary uric acid/creatinine ratio (5:3), inspiratory stridor due to laryngeal dystonia and frequently developed aspiration pneumonitis and bronchitis	g.151C>T (p. R51X)	Allopurinol (dose-20 mg/kg/day), potassium citrate, sodium citrate, gabapentin (40 mg/kg/day) and risperidone (up to 0.05 mg/kg/day at 34 months). The exact mechanism by risperidone helps/lowers SIB tendencies is debatable, since it has many targets in the central nervous system. While SAMe refills the purine pool in brain and hence enhances brain function.	20 mg/kg/day	i) At 26 months of age, the boy's SIB gradually decreased, his head movements became more stable and he began picking things from both his hands. ii) Facial, oral and trunk movements improved. iii) The patient's laryngeal stridor resolved, and he did not experience many episodes of pneumonia or bronchitis. iv) When he was 26 months old, an MRI revealed no signs of brain atrophy or aberrant intensity. v) Uncontrolled bodily movements (dyskinesias) when agitated or annoyed.	(7)

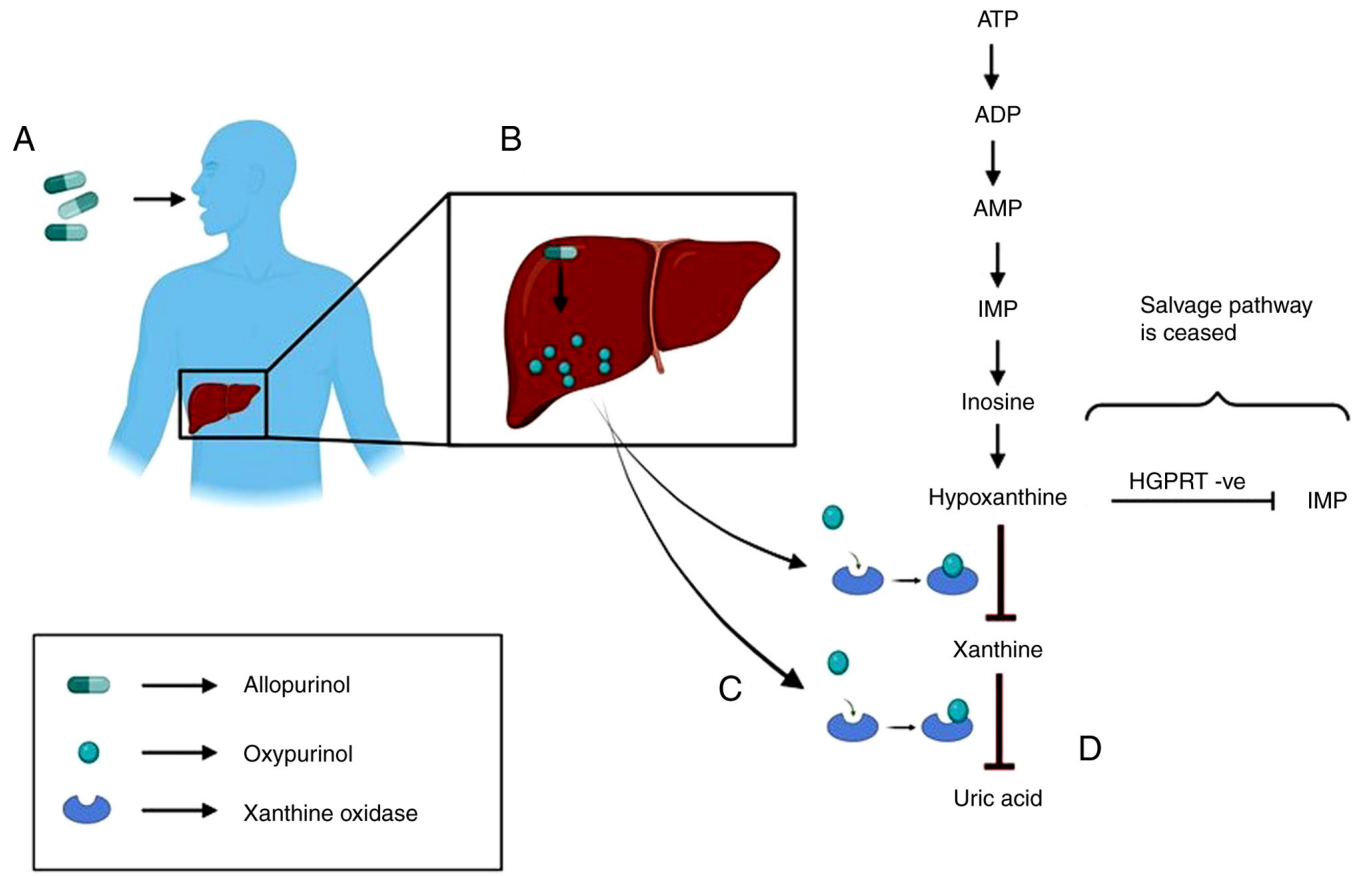

Figure 3. (A) Allopurinol when ingested (B) is converted into its active metabolite in the liver, oxypurinol which (C) inhibits the enzyme xanthine oxidase, thereby (D) lowering the levels of uric acid production. IMP, inosine monophosphate.

are yellow-colored lesions that form around joints. The tophi are composed of a uric acid (monosodium urate) core and skin that can become stretched and taut, sometimes to the point of ulceration. Allopurinol aids in the dissolution of tophi (81). However, higher concentrations of allopurinol are responsible for the formation of xanthine stones and oxypurinol-7-riboside, which causes derangement in the de novo synthetic pathway of pyrimidine by blocking the enzyme ornithine decarboxylase (82). As a result, orotidine 5' monophosphate begins accumulating and is rapidly degraded to orotidine, which cannot be degraded further and thus starts accumulating in RBCs and urine (Fig. 4) (83). To avoid xanthine stone deposition, it is advisable to have a high fluid intake to maintain a neutral or alkaline pH. Treatment with allopurinol did not correct the movement disorder or SIB. For example, in a study conducted on two male pediatric patients with a novel LND mutation, allopurinol normalized urate levels in RBCs and lowered serum uric acid levels, thereby lowering the risk of kidney stones, but did not help with movement disorder (2). Although allopurinol is very effective in maintaining urate levels, its downstream products, namely 5-OHisourate and allantoate, do not respond well to allopurinol.

Deep brain stimulation (DBS). DBS is a neurosurgical procedure that involves implanting electrodes in specific brain regions to control activity. The electrical impulses generated by these electrodes are controlled by an implantable pulse generator, which is fitted to the chest below the clavicle (beneath the skin) (Fig. 5) (84). DBS is used to treat neuropsychotic/neurological disorders, where medication has failed to provide any relief. Depending on the case profile of each individual, a physician/clinician determines the strength of the pulse to be delivered, the duration of the pulse, how long it should last, and how many times it has to be repeated for the patient to obtain optimal results (85). Achieving optimal effectiveness requires adjusting stimulation parameters, including voltage, pulse width and frequency (86). The exact mechanisms through which DBS functions are not yet fully understood. It is generally accepted that it functions by stimulating and/or inhibiting neurons that are in close proximity to electrodes. Low-frequency stimulation can excite the nearby cells. However, high-frequency stimulation tends to have an irreversible effect by lowering local activity (87). Four primary hypotheses have been proposed to explain the beneficial effects of DBS in movement disorders: Depolarization blockade, synaptic inhibition, synaptic depression, and modulation of abnormal oscillations in pathological networks (88). The globus pallidus (GP) is a subcortical triangular structure, present below the cerebral cortex, medial to the putamen. The main function of GP is to control voluntary movements and consciousness (89). Therefore, DBS of the GP is used to treat movement disorders (as in Parkinson's disease) and medication-resistant mental health conditions. Examples of such case studies are presented in Table IV (90,91).

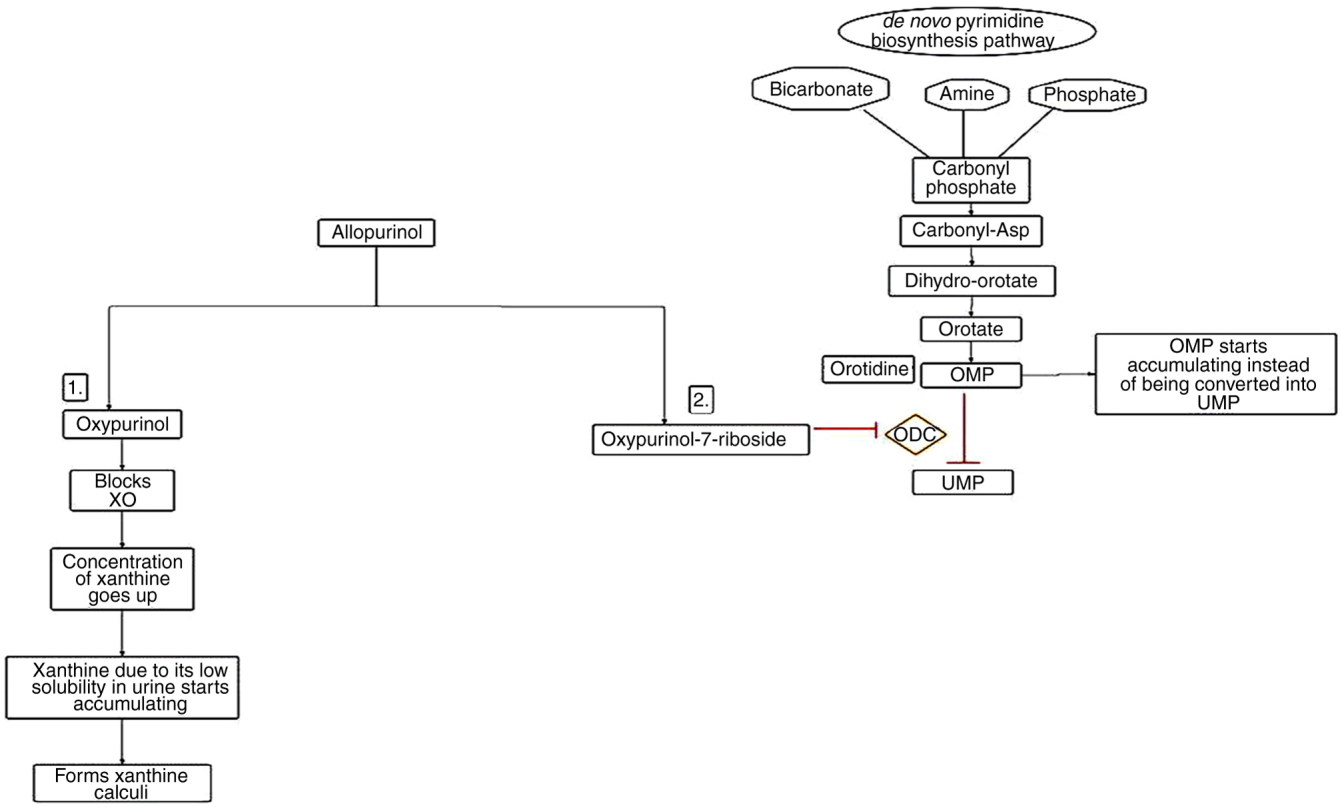

Figure 4. Allopurinol is converted into its active metabolite 1. Oxypurinol, higher concentrations of which are responsible for the formation of Xanthine stones and 2. Oxypurinol-7-riboside, which causes a derangement in de novo synthetic pathway of pyrimidine, by blocking the enzyme ODC. As a result, OMP begins accumulating and is rapidly degraded to orotidine, which cannot be degraded any further and thus starts accumulating in the RBCs and urine. XO, xanthine oxidase; OMP, orotidine 5'monophosphate; UMP, uridine monophosphate; ODC, ornithine decarboxylase.

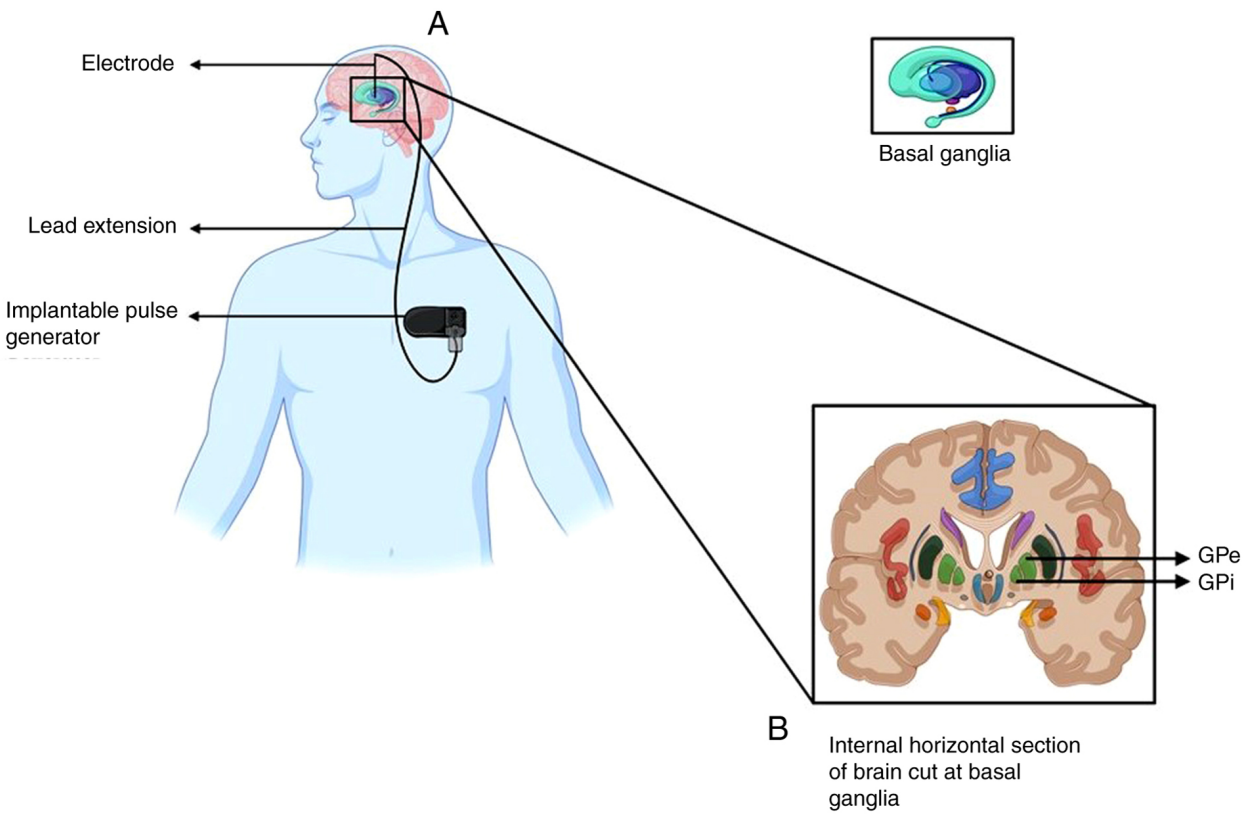

Figure 5. Deep brain simulation: (A) An electrode is fitted in the globus pallidus region of the basal ganglia. An insulated lead wire connects the electrodes to a neurostimulator device called implantable pulse generator, which is implanted beneath the skin, just below the clavicle bone; (B) the globus pallidus comprises of two segments, GPi and Gpe. GPi, globus pallidus internus; GPe, globus pallidus externus.

Table IV. Case studies of DBS in LNS identified in the literature.

Age and sex of the patient(s)	DBS Site	Symptoms	Other treatments	Outcome	(Refs.)
15 years/male (age at diagnosis, 3 years)	Bilateral chronic stimulation of the middle area of Global Pallidus Internus (GPI)	Dystonic postures and sporadic involuntary movements and had trunk opisthotonos	Levodopa with no benefits	i) Dystonic involuntary movements vanished and opisthotonus improved. ii) After 3 months follow up, the boy's parents reported that self-mutilative behaviors have completely disappeared and he no longer needed physical restraints. iii) Follow up was done again at 24 years, which revealed that the boy had still not developed self-mutilative behaviors. These results suggest that the SIB is either due to dysregulation in basal ganglia pathway or is secondary to the dystonia.	(90)
Two patients; ages, 12 years (age at diagnosis, <1 year	Anterior and posterior parts of the globus pallidum	Dystonia and self-mutilative behaviors	Patient 1 was on risperidone, gabapentin, carbamazepine, amantadine and clonazepam together with allopurinol, and patient 2 on a combination of diazepam, clobazam and sodium bicarbonate	Electrophysiologically, a silent zone was observed between -4.3 and -3.2 mm from the target, illustrating the transition between the GPE and the GPI. 56 GPE neurons and 106 GPI neurons underwent micro-recordings. Within 3 months post-operation, a number of their self-injurious behaviors vanished and their limbic dystonic movements significantly diminished, as a result of which they no longer needed high doses of medications.	(101)
16-year-old, male (age at diagnosis, 6 months)	DBS of motor and limbic regions of the GP was suggested. To treat SIB limbic circuit in the antero-ventral part of the GPI was targeted, and to help with dystonia and dyskinesia, the sensorimotor part of the GPI was selected. The stimulation was given at a frequency of 130 Hz and pulse width of 450 msec. For both limbic and motor leads, voltage was increased up to 1.6 V.	Slurred speech, SIB, cerebral palsy, dystonia of the limbs, trunk and head and hypotonia	Baclofen, diazepam, clomipramine, and cyamemazine	The changes in dystonic movements were assessed post and pre-operatively, using the Burke-Fahn-Marsden Dystonia Rating Scale. Similarly, SIB was assessed using the Behavior Problems Inventory (BPI-01). i) Improved aggressive behaviors and dystonic disorders. ii) DBS efficacy was maintained after 28 months. iii) The quality of life of the patient and of his family was dramatically improved. iv) At rest, the four limbs are not tied to the bed and to the wheelchair, and protection of the fingers by the gloves is not necessary anymore. Bilateral simple manipulations are possible.	(102)

Table IV. Continued.

Age and sex of the patient(s)	DBS Site	Symptoms	Other treatments	Outcome	(Refs.)
10-year-old boy	Single-channel generators connected to a single electrode on each side of his brain.	Presented at 8 months of age with poor muscle tone, at 12 months of age cerebral palsy was detected and at 15 months of age involuntary movements started. At 22 months of age, he was diagnosed with LNS. His SIB began at 4 years of cell with biting if fingers and lower lip, that was so severe that he had to get his primary teeth removed and used elbow restraints. At age 7, there was a fatal episode of dystonia that lead to hyperthermia, rhabdomyolysis (the muscle fibers breakdown, and its components such as myoglobin, creatine kinase (CK), aldolase, and lactate dehydrogenase, as well as electrolytes, into the extracellular space and into the blood flow) and transient renal impairment.	Intrathecal baclofen pump, baclofen	Barry-Albright Dystonia Scale was used to assess his progress. Within 3 months of treatment, he gathered control over his bodily movements and SIB resolved completely. Physical restraints were no longer needed and his lips were healed.	(103)

Table IV. Continued.

Age and sex of the patient(s)	DBS Site	Symptoms	Other treatments	Outcome	(Refs.)
29-year-old male (age at diagnosis, 14 years)	DBS of the GPI was suggested	Dystonia, ambulation disorder and SIB	Allopurinol 400 mg/day; baclofen 40 mg/day; clonazepam 10 mg/day; L-Carnitine 2 tablets/day; clozapine 450 mg/day; carbamazepine 1,600 mg/day; paroxetine 40 mg/day; gabapentin 1,800 mg/day; amytripline 75 mg/day; risperidone 6 mg/day; olanzapine 20 mg/day; thyoridazine 500 mg/day	His progression was assessed using the Burke-Fhan-Marsden Dystonia Rating Scale (BFMDRS) and the Mean Disability Scale (MDS) after the operation at 3, 6, 9 and 12 months, and every 6 months thereafter. i) Right away after starting the bilateral stimulation, his SIB was under control and the caretakers no longer needed to tie his hands or put gloves. ii) After the 2nd month, his dystonic movements markedly improved. The pulse generator was switched off 10 days after the DBS was started, and as expected self-harming behavior and dystonic symptoms returned. On the same day, electrical stimulation was started again and the benefits resumed. Since then, stimulation was not stopped. The benefit of stimulation persisted during the five-year follow-up and is still present now.	(91)

CRISPR-mediated gene correction. This approach focuses on correcting the mutant HGPRT gene in individuals with LNS. To check the functionality and reliability of this procedure, researchers first developed an LNS disease model using human near-haploid cells (HAP1 cells). Human near-haploid (HAP1) cells were created from the chronic myelogenous leukemia cell line, KBM-7, which was obtained from a male patient; hence, it did not have a Y chromosome; as a result, haploid HAP1 cells have one X chromosome (92). The researchers opted to work with this particular cell line due to the following reasons: i) These are of human origin; hence, the results generated would be much more accurate compared to non-human cell lines; ii) these are haploid in nature; iii) the HAP1 cell line is the optimal model for genetic manipulation as these cells have a high transfection efficiency and responsiveness to CRISPR-based editing techniques; and iv) this allows researchers to induce specific mutations and study the underlying pathophysiology in a controlled environment *in vitro*.

First, c.430C>T and c.508C>T mutations were introduced in HAP1 and 293T/17 cell lines using cytosine base editors (CBE). CBEs have a cytosine deaminase, which is a catalytically modified cas9 enzyme that can carry out the transition of C:G to T:A, whereas adenine base editors (ABEs) induce the transition of A:T to G:C and contain a catalytically modified cas9 adenine deaminase. These were then successfully corrected using ABEs, demonstrating the potential of base editing for gene therapy (93,94). Not only did it correct the mutation, it also rendered the *hgprt* gene functional. In HAP1 cells, mutations can be fixed using ABEs.

According to this study, ABEmax-SpG was able to repair the c.508C>T mutation by as much as 5.2% without resulting in bystander mutagenesis (20). ABEmax-xCas9(3.7) also repaired the c.430C>T mutation by up to 3%. These findings demonstrate the efficaciousness of ABEs in correcting particular HGPRT1 mutations in HAP1 cells, while in 293T/17 cells the correction efficiencies were observed to be as high as 3% for the c.430C>T mutation and up to 5.2% for the c.508C>T mutation, with only minimal bystander mutagenesis occurring within the active window of base editing. highlighting their potential for therapeutic gene editing applications.

Second, the c.333_334ins(A) mutation was introduced using prime editors (PEs) in HAP1 cell lines using prime editing guide RNA (pegRNA) designed for this specific mutation. The same mutation was also present in patient-derived fibroblasts. Patient-derived fibroblasts were used to interpret and analyze the applicability of this approach in a clinically relevant context. This pegRNA guides the PE to the site of the gene where changes must be made. Whatever correction/change needs to be induced, the sequence for that is present in the pegRNA. This specific mutation was found in a 9-year-old male pediatric Korean patient with LNS, which mimicked this mutation in the HAP1 cell line and 293T/17 cells, and this was successfully corrected using PE, although the efficiency varied (20). Mutations in 293T/17 cells could be corrected only up to an efficiency of 50%, whereas it was much lower in patient-derived fibroblasts (only 14%). Similarly, it was also shown that adenine and cytosine BEs corrected mutations without DNA cleavage, while improved PEs achieved up to 14% correction in fibroblasts with minimal off-target effects, highlighting their potential as therapeutic tools for this rare genetic disorder (20).

5. Conclusion and future perspectives

It is indispensable to understand the etiology of the disease to develop effective treatments. Understanding the mechanisms associated with drugs that have shown positive outcomes in most patients will also help in the development of new drugs that can be administered either alone or in combination. For example, DBS appears to work well for young pediatric patients, although contradictory results have been observed in adult patients. Therefore, further intensive research is required to better understand the exact working mechanisms of these approaches. Although this is a rare disease, clinical trials need to be conducted using drugs that have shown effective results in the majority of patients. For example, two studies demonstrated that a double-blind placebo-controlled study could be employed to help generate meaningful data from a small number of subjects (95,96). Models that can replicate the complete biochemical picture of HGPRT deficiency in the human brain should also be developed. Stem cells and HAP1 cells have made it easier to carry out *in vitro* investigation/study of the underlying mechanisms in neurons, which is otherwise not possible. Similarly, to reduce the toxicity of high allopurinol levels, other xanthine oxidase inhibitors, such as febuxostat, should be considered. Utilizing new models in combination with cutting-edge investigative techniques can offer a greater understanding of the etiology and promising therapeutic options against LNS.

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Availability of data and materials

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Authors' contributions

DV conceptualized the study and was also involved in the literature search and the selection of studies for the review, as well as in the writing and preparation of the original draft of the manuscript. CJ and MP prepared the tables and were also involved in the literature search. RG supervised the study and edited the manuscript. All the authors have read and approved the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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