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Review Article

METABOLIC DISORDERS: LESCH-NYHAN SYNDROME

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ABSTRACT

Lesch-Nyhan syndrome is a condition characterized by neurological and behavioral abnormalities and the overproduction of uric acid in the body. According to one estimate, the disorder occurs at a rate of approximately 1 in 400,000 births in the world. It occurs almost exclusively in males due to being an X-linked recessive disorder. Excess uric acid production and Neurological disorders with characteristic self-mutilating behaviors are major symptoms of LNS. LNS is a rare inborn error of purine metabolism characterized by the absence or deficiency of the activity of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT), Mutations in the HPRT1 gene cause LNS. Treatment for LNS is symptomatic, Gout treated with allopurinol; Kidney stones with lithotripsy; No standard treatment for the neurological symptoms of LNS.

Keywords: Lesch-Nyhan syndrome, Neurological, Uric acid

1. INTRODUCTION

If an abnormal or irregular chemical activity in the body causes disruption in natural metabolism which, combined with several other effects, ends up affecting the regular operation of the body is considered a metabolic disorder. Hereditary metabolic diseases are a source of metabolism that arises because a faulty gene causes an enzyme defect/deficiency. These diseases are termed as inborn errors of metabolism and have several subtypes. Inborn metabolism errors represent a large majority of inherited disorders and congenital metabolism abnormalities. Most of these are caused by single-gene defects which code for enzymes to allow conversion to different products. For the plurality of conditions, issues occur owing to the buildup of substances or the consequences of insufficient synthesizing of important compounds. Lesch-Nyhan Syndrome (LNS) is one such disorder.

Lesch and Nyhan in 1964 [1], observed two brothers with a disorder that had characteristic symptoms including hyperuricemia, extreme uric acid output, choreoathetosis, striking mental and development failure, spasticity, and self-mutilation. Three years later, Seegmiller, Rosenbloom and Kelley [2] identified the practically "complete" deficiency (hypoxanthine-guanine) of purine metabolizing enzyme Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) in the skin and erythrocyte lysate from some patients (the IMP) for which some authors have used the nomenclature inosine monophosphate (IMP) phosphoribosyltransferase [3]. The deficiency of an enzyme in other tissues was also verified by closely impaired patients [4].

Many patients who are hyperuricemic and generate excess uric acid, but "partially" lack the HGPRT enzyme [5-9] have since been identified. Many patients suffered from gouty arthritis and hyperuricemia, while "fully" impaired patients experienced severe neurological symptoms. All of these disorders, which are caused by HGPRT deficiency, involve a different subset of the hyperuricemic population. The subject of this analysis is the condition with a complete enzyme deficiency.

1.1. Enzyme defect

Hypoxanthine-guanine phosphoribosyltransferase catalyzes the conversion of hypoxanthine to inosinic acid and guanine to guanylic acid in the presence of phosphoribosylpyrophosphate (PP-ribose-P) [10, 11] (fig 1).

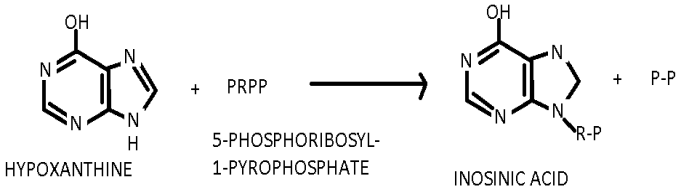


Fig.1: The reaction catalized by hypoxanthine-guanine phosphoribosyl transferase illustrated with hypoxanthine as substrate.

The natural purine base, xanthine, as well as several purine analogues, including 6-mercaptopurine, allopurinol, 8-azaguanine, and 6-thioguanine, are also substrates for the enzyme [12,13]. The enzyme is activated by magnesium ions and is inhibited by the products of the reaction. Guanylic acid and its di- and triphosphates are much stronger inhibitors than inosinic or xanthylic acid [13].

Patients observed with Lesch-Nyhan syndrome had no detectable activity of the HGPRT enzyme in their erythrocytes or their tissues in the autopsy. Despite having no detectable enzyme activity, almost all the patients with LNS did have a protein which exhibits cross-reactivity (CRM+) with an antibody to the normal enzyme [14]. This indicates that the mutation responsible for functionally complete deficiency of this enzyme is present on the structural coding gene of the enzyme.

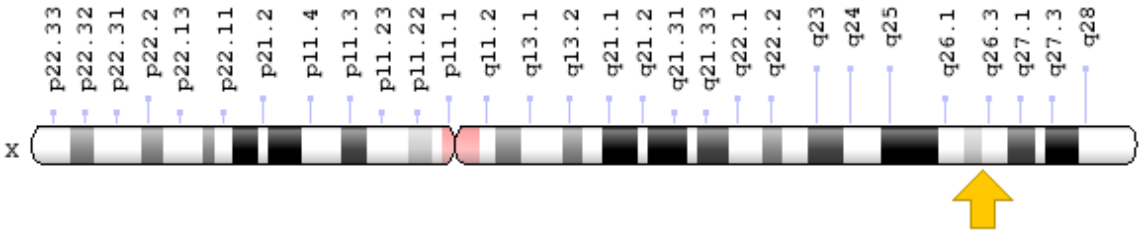
Fibroblasts cultured from a number of patients had little but detectable levels of HGPRT activity [15, 16]. On a detailed examination of the mutated enzyme isolated from fibroblast culture, it was observed to have at least three different phenotypes (table 1).

Table-1: Genetic heterogenicity of hypoxanthine guanine phosphoribosyl transferase deficiency in fibroblast derived from patients with Lesch-Nyhan Syndrome [16]

	Product Inhibition	Thermal Stability	Prototype (cell strain)
Normal Mutant	+	+	
Suspect 1	+	+	193
Suspect 2	+	-	182,197,198,199
Suspect 3	-	-	121

(+ve Normal, -ve Abnormal)

These studies [16] provided for the additional evidence that the mutation responsible for the disorder is present on the structural gene for the HGPRT enzyme. And mutations probably aren't large deletion or frame shift, but single nucleotide point mutation causing the mutation of single amino acid.



This figure is available through: https://ghr.nlm.nih.gov/gene/HPRT1#location

Fig. 2: The HPRT gene has 9 exons. The HGPRT1 form of an enzyme known as hypoxanthine-guanine phosphoribosyltransferase 1 is given with instructions by HGPRT1 gene. Cellular recycling of purines is possible with this enzyme. The Lesch-Nyhan syndrome was found with more than 200 mutations within the HPRT1 gene. These mutations include alterations of single DNA (nucleotide) building blocks, or the addition or elimination of minor amounts of DNA within the gene. Such modifications contribute to hypoxanthine phosphoribosyltransferase 1. Either non-functional or very low-functional [17].

2. CLINICAL DESCRIPTION

Patients with HGPRT deficiency appear to be normal during birth; their first symptom usually is the observation of the orange crystals in the diaper of the infant or crystalluria with urinary tract obstruction. Other rather uncommon symptoms include renal failure, acidosis, or severe vomiting. Psychomotor delay (if present) becomes observable within 3-4 months of the birth. Self-mutilation, in the form of lip biting or finger chewing, might appear as soon as the teeth are present [18, 19].

2.1. Hyperuricemia-related renal and articular symptoms

Symptoms of this type are found in all persons that have HGPRT deficiency (partial or complete). The severity of the enzyme dysfunction is unknown. The common gout symptoms (acute inflammation, tophi, nephrolithiasis or urolithiasis, and renal disease) may be present. The orange crystals in the diaper, crystalluria during the first years of childhood or juvenile arthritis are observed in the descriptions of hyperuricemia. If diagnosis and

treatment delays, allopurinol can only be used to relieve gouty symptoms and renal dysfunction.

2.2. Neurological symptoms

Neurological symptoms are differentiated between the HGPRT deficient patients; the ones with the "complete" deficiency of the enzyme get severely affected by neurological symptoms and can become dependent on others for the day to day activities too. Neurological symptoms affect the motor sphere, cognitive, and behavioral aspects.

2.3. Motor sphere

H. A. Jinnah *et al*. [18], explained that the motor syndrome of complete HPRT deficiency is best classified as severe action dystonia, superimposed on baseline hypotonia. Dystonia uniformly affects all the parts of the body and its severity may lead the patient to be unable to stand or walk and leave them confined to the wheelchair. Involuntary movements such as choreoathetosis and ballismus are usually present but are not evident at rest. These symptoms are associated with voluntary movements and increase with excitement and anxiety. Dysarthria, dysphagia, and opisthotonus are frequently reported. Corticospinal tract signs such as spasticity, hyperreflexia, and extensor plantar reflex are generally reported in later years and they may reflect an acquired defect.

In partial HPRT-deficient patients, the grade of dystonia is less severe and appears in the form of a dystonic gait, speech difficulties, exercise-induced dystonia, or is unapparent.

2.4. Cognitive impairment

The first definition of Lesch-Nyhan included mental delay as a syndrome function. Complete HPRT deficient patients, though, exhibit slight to moderate intellectual deficiencies when tested with basic movement disorders examination. Such patients display a lack of focus, but the balance of the non-verbal knowledge is well preserved [20, 21]. Partial HPRT deficient patients deficits may undergo differing degrees of mental retardation, including relatively average intelligence [20].

2.5. Compulsive self-injurious behavior

The most surprising characteristic of Lesch-Nyhan syndrome is that it can only be observed in patients with full enzyme deficiencies, though patients with Lesch-Nyhan are rarely autonomous. Patients start biting their mouths, their tongues or their fingers and major automatic lesions may occur without restrictions [22, 23]. A loss of sensation does not result in mutilation (patients experience discomfort and are relieved when they are protected). In some instances, abusive and violent behavior is against friends and family too, including spitting, screaming, or use abusive language. Self-mutilation may start between 2 and 16 years of age and, in some instances, is associated with or aggravated by psychological stress (adolescence, familial conflicts). While Lesch Nyhan patients are often content and engaged children when restraint of their violent behavior. A variety of environmental variables, including education [24], will substantially modulate the neurobehavioral condition. Partial victims are not self-injured, but the obsessed-compulsive disorder has been identified in some cases.

2.6. Uric acid overproduction

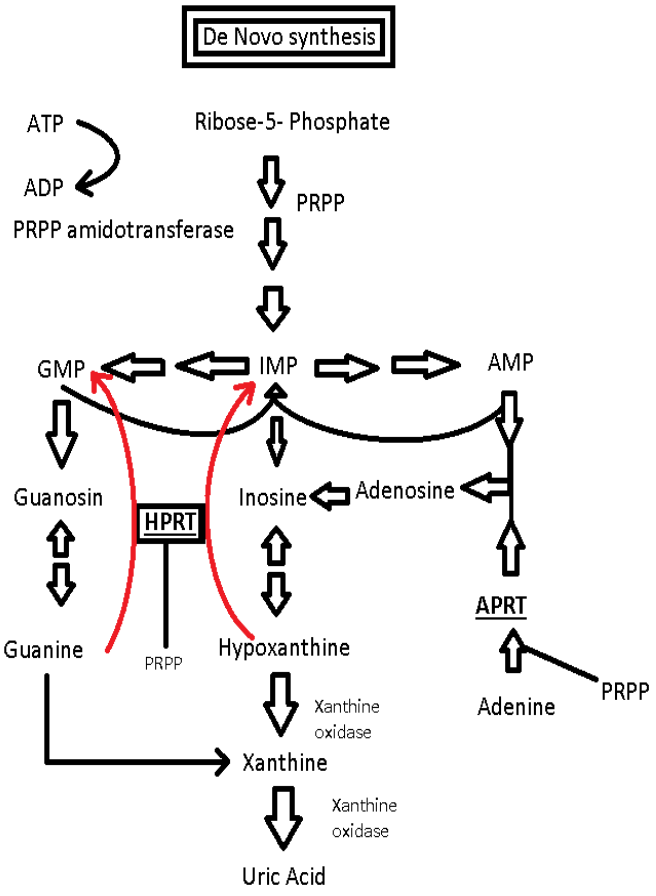


Fig. 3: Purine metabolism. The metabolic scheme shows the first and rate-limiting step of *de novo* purine synthesis mediated by the enzyme 5'-phosphoribosyl-1-pyrophosphate (PRPP) amidotransferase and the hypoxanthine phosphoribosyltransferase (HPRT) and

adenine phosphoribosyltransferase (APRT) mediated salvage pathway. The de novo synthesis occurs in a multi-stage process that calls for the synthesis of inosine monophosphate (IMP) molecule by four amino acids, one PRPP, two folates and three ATPs. HPRT catalyzes the salvage synthesis of inosine monophosphate (IMP) and guanosine monophosphate (GMP) from the hypoxanthine and guanine purine bases, using PRPP as a co-substrate, respectively. The HPRT defect results in the accumulation of its substrates, hypoxanthine, and guanine, which are converted into uric acid utilizing xanthine oxidase. Elevated APRT activity may also contribute to purine overproduction.

Several mechanisms can be identified that contribute to uric acid overproduction in HPRT deficiency [25, 26].

a. HPRT catalysts the salvage syntheses, using 5'-phosphoribosyl-1-pyrophosphate (PRPP) as a co-substrate of inosine monophosphate (IMP) and Guanosine monophosphate (GMP) from the purine basis, hypoxanthine and guanine, respectively. The hypoxanthine and guanine deficiency of HPRT causes an accumulation of its substrates, which is converted by xanthine oxidase in uric acid.
b. Purine synthesis rises with the expanded abundance of PRPP in PRPP amidotransferase, the de novo enzyme synthesis of purine nucleotides (Fig. 3).
c. PRPP amidotransferase feedback inhibitors, IMP and GMP are reduced, on the other side. This dual pathway results in an increased purine nucleotide de-novo synthesis. The combination of poor purine basis recycling with increased purine nucleotide synthesis leads to overproduction of uric acid in HPRT deficiency. The increased activity of APRT can also lead to overproduction of purine.

2.7. Pathophysiology of neurological symptoms

The pathophysiology of the neurological and behavioral dysfunctions remains unclear. No characteristic physical abnormalities were observed in the *post-mortem* of the Lesch-Nyhan syndrome affect diseased patient's brain [27, 31]. Pioneer neurochemistry analysis of *post mortem* tissues revealed the first biochemical evidence of dysfunction of brain neurotransmitters in Lesch-Nyhan syndrome. In this study, biochemical aspects of the function of dopamine-neuron terminals in the striatum were decreased, whereas serotonin and 5-hydroxyindoleacetic were increased [28]. Additional biochemical studies in the cerebrospinal fluid of the Lesch-Nyhan patient show a decreased levels of the homivanillic dopamine metabolite and higher levels of hypoxanthine and xanthine [27, 29, 30]. In recent in vivo studies on human ligands in the brain, using positron-emission tomography, have confirmed changes in the dopaminergic system in Lesch-Nyhan patients [32, 33].

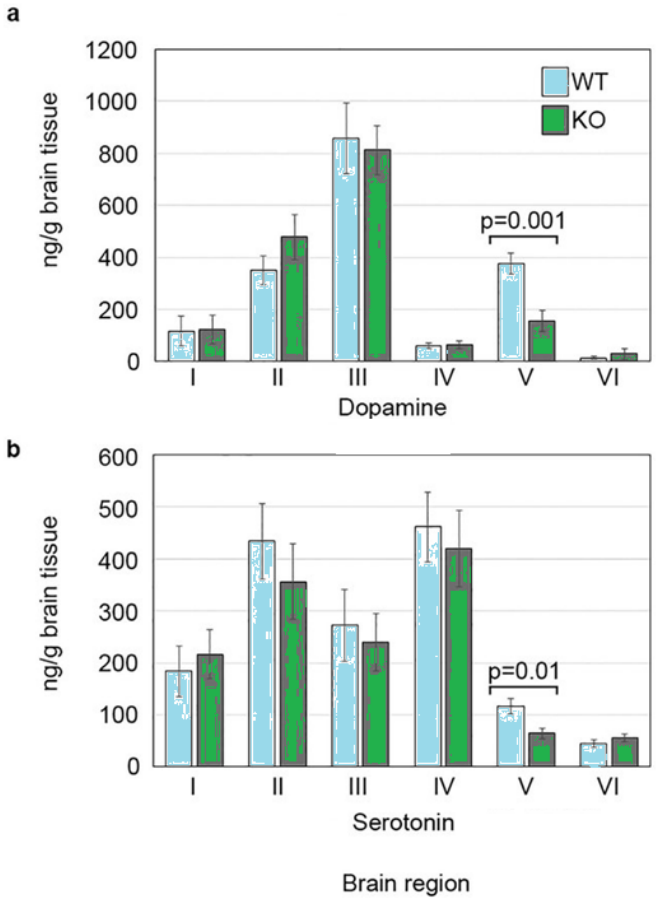


Fig. 4: (Source: Reduced levels of dopamine and altered metabolism in brains of HPRT knock-out rats: a new rodent model of Lesch-Nyhan Disease, April 2016 Stephen Meek, Alison Thomson et al.[34]). HPRT deficiency effect on rat brain dopamine and serotonin levels. In wild-type brains and HPRT knock-out (KO) rats, HPLC analyzes (a) dopamine and (b) serotonin in regions I – VI. The y-axis value represents the means obtained from the analysis of nine types and 7 HPRT KO brain samples + /−SD. White and grey bars represent the control type of the wild and KO values, respectively. (Its size is: Olfactory bulb, II: hypothalamus, III: pre-frontal cortex, IV: midbrain; V: hipposcope, cortex, and striatum. VI: brain cerebellum). Summarizing, several studies have suggested that Lesch-Nyhan syndrome neurological symptoms might be associated with dopaminergic system dysfunction in the basal ganglia. The relationship between dopamine deficit and the purine metabolic disorders is still unknown

3. TREATMENT

3.1. Treatment related to Urine and Hyperuricemia

Several forms of therapy have been put forward and used, although no consistently successful results have yet been observed and criteria for efficacy are difficult to assess. Each of the different cases represents different biochemical abnormality and therefore requires a unique approach. The only symptom that is readily available to treatment is hyperuricemia with gouty arthritis and hyperuricemic neuropathy [35, 36]. Both of these clinically serious symptoms of the condition can be treated with the use of allopurinol [37]. As a result of the use of allopurinol (xanthine oxidase inhibitor), the concentration of uric acid in the serum and urine is lowered and the level of oxypurines is elevated [38].

The control of uric acid level in the serum and urine does not prevent the other serious characteristic of the LNS i.e neurological disorder [39], the most crippling part of which is the choreoathetosis, which may be serious enough to lead a patient to malnutrition and submit to infections.

The role of self-mutilation demands different attention due to not being directly related to spasticity and choreoathetosis, and it might respond differently to the therapy. It has been suggested [40] that these patients may have a low threshold of the activation of mechanisms for the repetitive and self-hurting behaviors. Therapeutic attempts should focus on both self-mutilating behavioural patterns and changes in the central nervous system. This particular trait seems to be most varying with respect to the patient's environment, equanimity, and his/her self-mutilating behavior.

Some evidence has come to surface that neurological disorders may have taken place *in utero* as a subsequent result of the metabolic disorder [41]. There is still doubt about the nature of the neurological disorders associated with the LNS, whether it is the outcome of a deficiency or if it is an overproduction disease. Therefore treatment needs to be focused on keeping both the possibilities in mind.

If the principal symptomatology arises from the failure of feedback inhibition of the first step in purine biosynthesis, the condensation of glutamine with 5-phosphoribosylpyrophosphate to give 5-phosphoribosylamine, then it is possible that this feedback inhibition could be re-instituted and the availability of 5- phosphoribosylpyrophosphate could be decreased by feeding adenine to the patients, providing that allopurinol is also administered to prevent the formation of 2,8-deoxyadenosine, which has nephrotoxic properties [42,43]. Nevertheless, the administration of adenine, diaminopurine, and inosine had no visible effect on the central nervous system malfunction [44, 45].

At the symposium held in Montreal in 1971, Winter [46] also reported that the administration of adenine therapy along with folic acid reduced the daily turnover rate of uric acid (still above normal) and elevated the level of glutamine in the cerebrospinal fluid without any detectable improvement in neurological dysfunction nor any reduction in the concentration of uric acid in serum.

Nicotinamide can also help to deal overproduction of uric acid [47]. It utilizes phosphoribosylpyrophosphate (PRPP) to convert into nicotinic acid mononucleotide and therefore consumes the excess PRPP. This therapeutic approach was used by Mongeau [48] for the treatment of a child with spasticity and dystonia with hyperuricemia and a deficiency of HGPRT in erythrocytes and cultured skin fibroblasts. Treatment with nicotinamide (500 mg twice daily) for 5-6 months without allopurinol did not affect the reduction of the patient's serum uric acid level of 10 mg/100 ml, and his symptoms remained unchanged too.

When the therapeutic approach associated with diminishing the cells available with PRPP fails to slow down the production of purine metabolism, a possible explanation could lie in the observations by Greene and Seegmiller [49] and by Fox and Kelley [50] that the concentration of PRPPin erythrocytes of the patients with the LNS is approximately 10 times greater than the normal subjects and hence reduction of the intracellular PRPP concentration might not be enough to affect a maximal overproduction of purine intermediates unless a drastic reduction is achieved.

Another approach to therapy would be to believe that even with an overall increase of purine synthesis, necessary nucleotide intermediates were deficient due to the failure to recycle hypoxanthine back to IMP. This possibility was investigated by Ghadimi et al., [51] who discovered in one patient the level of glutamine was lowered with respect to the normal subjects and figured that this could be corrected by adding monosodium glutamate (10g/24hrs) to the diet. The patient's protein intake increased as well as his well-being and improvement in neurological symptoms. During this time, for a period allopurinol was given to him and for the other part, he was given the placebo capsules.

Variations in the allopurinol treatment did not affect the symptoms but allopurinol is advisable for hyperuricemia.

To initiate a rational form of therapy, further new information is required to link the well-described enzyme related disorders to the development of clinical syndromes. Essentially all the analytical procedures are now available for either antenatal or neonatal diagnosis based on a suitable screening program, so there is a high probability that the devastating neurologic consequences of the disease could be averted if metabolic correlates between the enzyme defect and the clinical syndrome could be defined.

3.2. The Effect of S-Adenosylmethionine Treatment on Neurobehavioral Phenotypes in Lesch-Nyhan Disease

SAMe, a major methyl donor affects the CNS function by cellular transmethylation pathway, including the methylation of DNA, histones, protein phosphatase 2A, and several catecholamine moieties. SAMe has a well known antidepressant effect, and some investigators reported a functional effect in mouse models of Alzheimer's disease, epilepsy, and amyotrophic lateral sclerosis. The pathophysiology of LND is not completely understood; however, it likely involves cellular adenosine depletion. SAMe may reload the purine pool by serving as an adenosine donor. Adenosine can be formed into adenosine monophosphate by adenosine kinase and adenosine triphosphate. Adenylosuccinatelyase can form inosine monophosphate, which is then transformed into guanosine monophosphate by isocitrate dehydrogenase and replenishing guanosine triphosphate purines.

In a case presented by Kumamoto University, a child with dystonia and self-injuring behaviour was given a combination of SAMe and risperidone treatment which resolved his recurrent self-injuring behaviour. Although he often experienced inspiratory stridor due to his laryngeal dystonia and had frequent episodes of aspiration pneumonitis and bronchitis, he was free of inspiratory stridor after SAMe treatment. At present, the patient still receives the combination SAMe (15-20 mg/kg/day) and risperidone (0.05 mg/kg/day) treatment.

Chen et al. [51] reported the effectiveness of SAMe treatment for self-injury and dystonia in children with LND aged 1 month to 12 years. Conversely, Dolcetta et al. [52] reported that SAMe treatment improved self-injury in only 3 of 13 patients with LND who were aged 18 years or older and worsen self-injury in 5 patients. The effects of SAMe on LND-related self-injury and dopaminergic neurons probably depend on the patient's age.

The effectiveness of SAMe for the treatment of involuntary movements in neural diseases other than LND is controversial. More research is required to determine the efficiency of SAMe for involuntary movement in other neural disorders.

4. CONCLUSION

Clinical characteristics of the HPRT deficit include the symptoms, neurological manifestations and haematological disorders and uric acid overproduction. Allopurinol (xanthine oxidase inhibitor), folic acid (reduces uric acid production) and nicotinamide (utilizes phosphoribosylpyrophosphate (PRPP) to convert into nicotinic acid mononucleotide and consumes the excess PRPP) (hyperuricemia), S-adenosyl- methionine(major methyl donor, influences central nervous system function through cellular transmethylation pathways) (SIB) are some effective drug to reduce the symptoms. There is no particular drug treatment available for both the main symptoms of the LNS, hyperuricemia with dystopia and neurological disorders. Different combinations of drug treatment are required for dealing with neurological disorders and different for the hyperuricemia and dystopia. Therefore there is a lot of scope for research and development regarding LNS to find an appropriate treatment to ease the symptoms in patients affected with it. Applications of enzyme transfer therapy and gene therapy can also be used to cure this error of metabolism completely.

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