BMJ Best Practice

Lesch-Nyhan disease

Straight to the point of care

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Summary

Lesch-Nyhan disease is an X-linked inborn error of metabolism caused by a deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT).

Characterized by hyperuricemia and a typical neurobehavioral phenotype, including a hyperkinetic movement disorder dominated by dystonia, attentional deficits, and behavioral disturbances with self-injury.

Should be considered when delayed development is accompanied by a hyperkinetic movement disorder, including dystonia, particularly when routine brain MRI is normal.

Should be suspected if a delayed development is accompanied by self-injurious behavior or evidence of excessive production of uric acid.

Diagnosis is based on HPRT enzyme activity, preferably measured in live cells such as cultured fibroblasts, and on molecular genetic techniques demonstrating the gene mutation. Results might provide predictive clues about ultimate disease severity.

Currently, no curative treatment is available. Supportive care includes muscle relaxants for the movement disorder, and physical restraints or teeth extraction to prevent self-injury.

Definition

Lesch-Nyhan disease (LND) is an X-linked inborn error of metabolism, caused by a mutation in the gene encoding the purine recycling enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT).[1] [2] The first description was in 1964, when two brothers originally diagnosed with cerebral palsy were later recognized as living with a previously undescribed inherited metabolic disease because of the familial occurrence and unusual clinical features.[1] HPRT deficiency causes overproduction of uric acid, which may lead to hyperuricemia, nephrolithiasis, gouty arthritis, and subcutaneous tophi.[3] In addition, patients exhibit a distinctive neurobehavioral phenotype, characterized by dystonia, attentional deficits, and behavioral disturbances including self-injury, presumably attributable to dysfunction of the basal ganglia dopamine system.[4] Patients with a partial enzyme deficiency (Lesch-Nyhan variants [LNV]) display an incomplete phenotype: overproduction of uric acid with or without neurologic dysfunction, and no self-injury.[3] [5]

Epidemiology

The estimated prevalence of Lesch-Nyhan disease (LND) ranges from 1 case per 235,000 to 1 case per 380,000 live births.[8] [9] LND has been reported in most ethnic groups, with approximately equal rates. Because of the X-linked recessive mode of inheritance, virtually all patients are male. LND may occur in females as a result of exceptional genetic aberrations, although few female patients have been described to date.[3] Most patients come to medical attention early in life, usually before 4 years of age.

The prevalence of partial hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is currently unknown.

Etiology

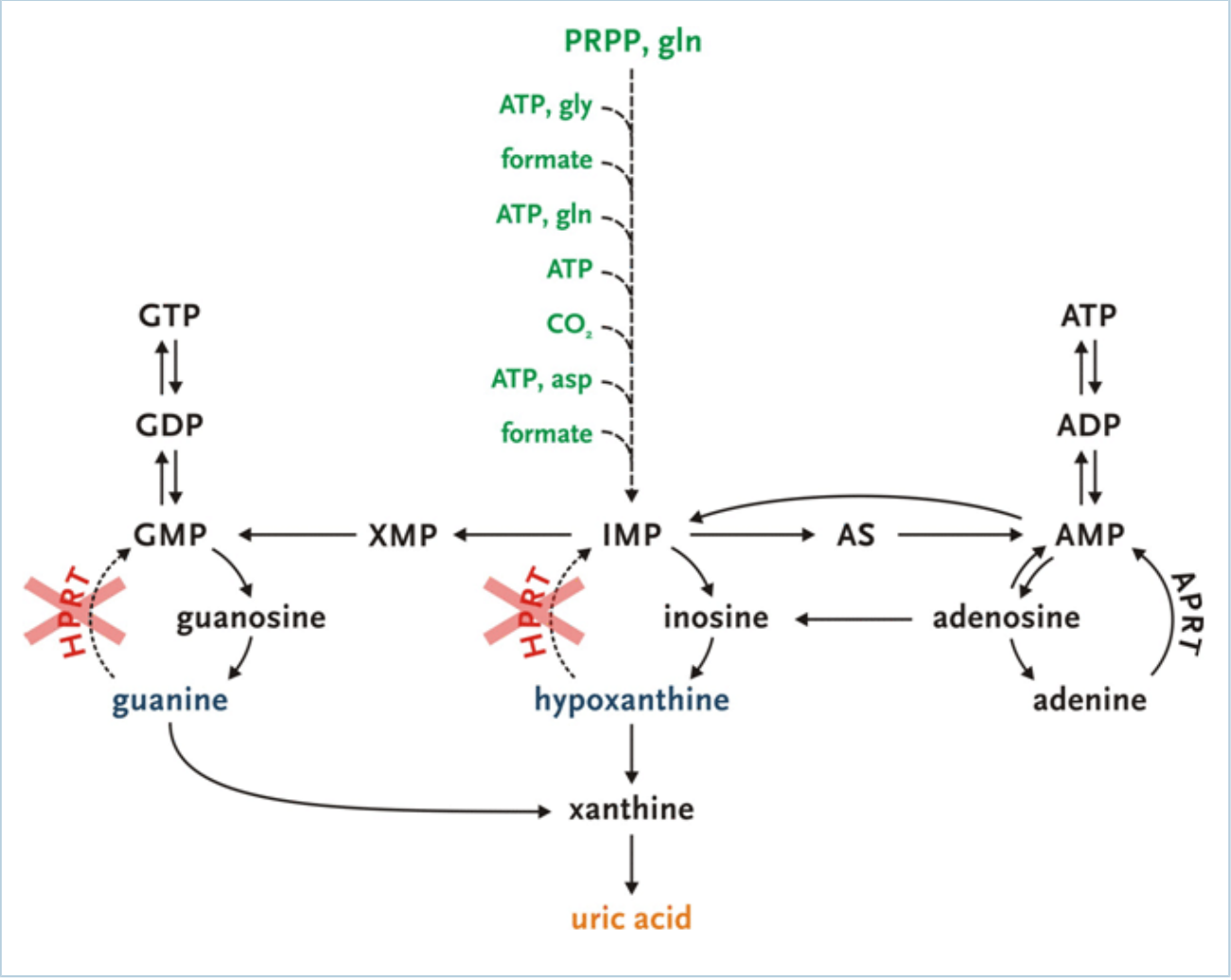
Lesch-Nyhan disease (LND) is caused by a mutation in the gene encoding hypoxanthine-guanine phosphoribosyltransferase (HPRT) on the long arm of the X-chromosome, at Xq26-q27.[10] The mutations are heterogeneous, including point mutations and other substitutions, deletions, and insertions.[11] [12] It is generally believed that the majority of mutations occur de novo, because classic LND males do not reproduce. Mutations causing disease appear throughout the HPRT gene, with some minor mutational hot spots. Genotype-phenotype correlations do not indicate that specific disease features are associated with specific mutation sites. In general, however, less severe clinical manifestations (Lesch-Nyhan variants [LNV]) result from mutations predicted to allow some degree of residual enzyme function.[11] [12] [GeneReviews: Lesch-Nyhan syndrome] (http://www.ncbi.nlm.nih.gov/books/NBK1149)

Pathophysiology

Hypoxanthine-guanine phosphoribosyltransferase (HPRT) mediates the recycling of hypoxanthine and guanine into their respective nucleotide pools. In the absence of HPRT, hypoxanthine and guanine are not recycled, but degraded to uric acid. The reduced purine salvage, together with an accompanying activation of de novo purine synthesis, causes marked overproduction of uric acid.[3]Despite this overproduction, efficient renal clearance limits average serum uric acid levels, which are typically increased less than two fold. The total renal uric acid excretion in classic Lesch-Nyhan disease (LND) is typically about four times that of controls. Chronic serum urate values >7.0 mg/dL are associated with an increased risk of deposition of urate crystals in joints, kidneys, and subcutaneous tissues.[13] If untreated, this may cause gouty arthritis, nephrolithiasis, and subcutaneous tophi.

LND is accompanied by a severe decrease in brain dopamine content in the basal ganglia, which is thought to be an important determinant of the neurobehavioral features, including the hyperkinetic motor disorder, attentional deficits, and abnormal behavior.[4] [14] [15] In addition, LND and Lesch-Nyhan variants (LNV) are associated with extensive abnormalities of gray matter and white matter that may also provide important clues to neural substrates of the phenotype.[16] [17] The exact relation between HPRT deficiency and dopamine dysfunction in LND remains unclear. However, evidence suggests an important relationship between purine recycling pathways and the neurochemical integrity of the dopaminergic phenotype, and a role for HPRT in neurodevelopmental processes has been implied.[18] [19] [20] Despite the dopamine deficiency, the effect of dopamine replacement therapy is inconsistent and generally unhelpful, presumably because of the development of dopamine receptor super-sensitivity and other neuroplastic changes.[3] [21] Some patients also develop spasticity and hyperreflexia, indicative of dysfunction of the corticospinal motor

system which may result from myelopathy caused by chronic forceful involuntary movements of the neck.[22] [GeneReviews: Lesch-Nyhan syndrome] (http://www.ncbi.nlm.nih.gov/books/NBK1149)



The role of hypoxanthine-guanine phosphoribosyltransferase (HPRT) in the grand scheme of purine metabolism

Created by J.E. Visser, MD, PhD and H.A. Jinnah, MD, PhD; used with permission

Measurement	LND			LNV						Controls	
				HND			HRH				
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Serum uric acid (mg/dL)	11.9	4.4	(88)	13.4	3.6	(28)	12.8	6.3	(35)	4.5	1.3
Urine uric acid/creatinine ratio	2.9	1.1	(18)	1.6	1.3	(5)	1.0	0.5	(24)	0.3	0.1
Urine uric acid excretion (mg/kg/day)	39.6	13.4	(27)	33.6	17.6	(8)	23.5	10.3	(10)	9.7	3.7

Uric acid levels in patients with classic Lesch-Nyhan disease (LND), patients with Lesch-Nyhan variants (LNV), and healthy controls. SD, standard deviation; HRH: hypoxanthine-guanine phosphoribosyltransferase (HPRT)-related hyperuricemia; HRD: HPRT-related neurologic disease

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Classification

THEORY

Lesch-Nyhan disease (LND), Lesch-Nyhan variants (LNV): HPRT-related neurologic disease and HPRT-related hyperuricemia[3] [5] [6]

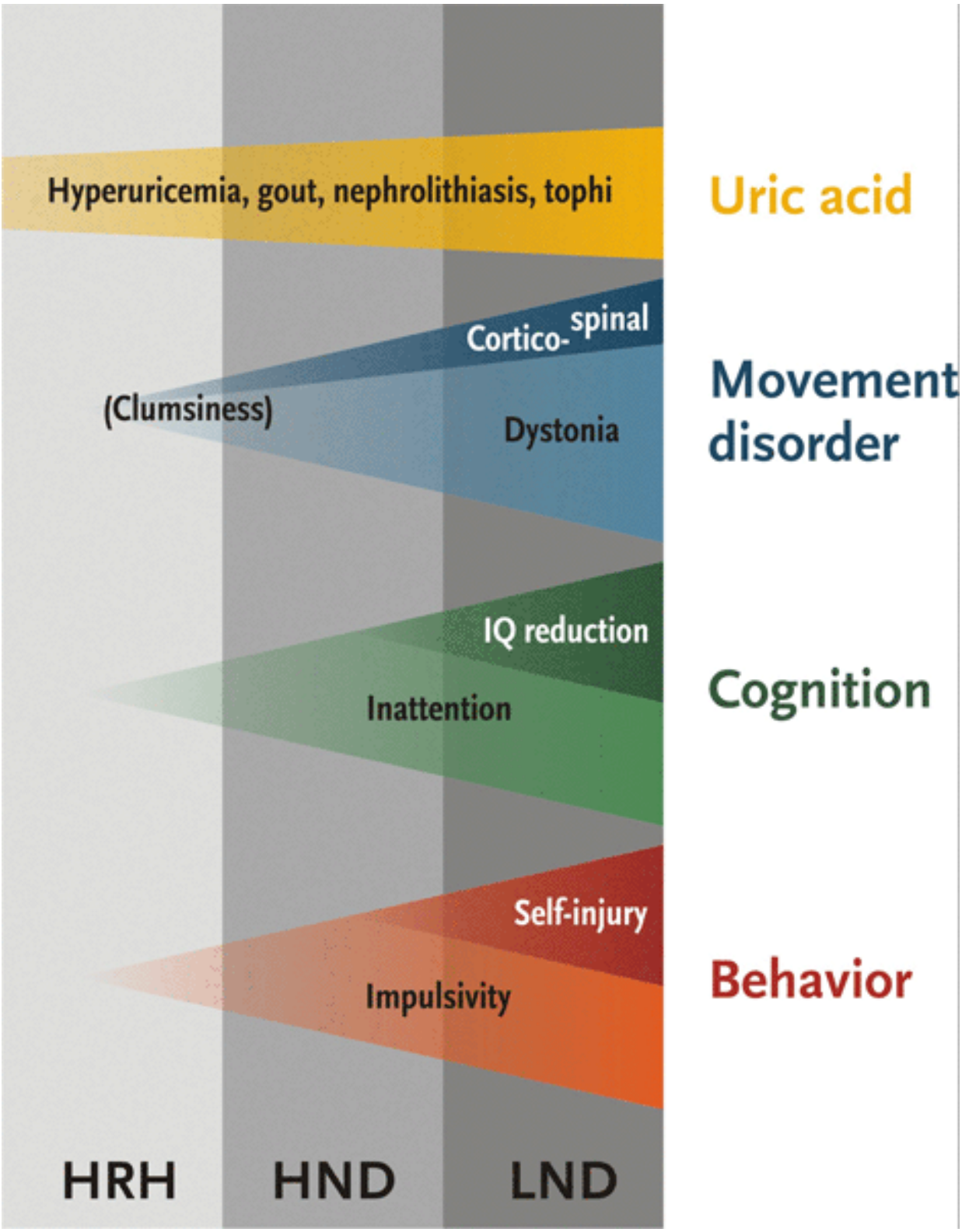
HPRT deficiency is associated with a phenotypic continuum, where the occurrence and severity of clinical features is dependent on the residual enzyme activity.

Classic LND patients, with virtually no enzyme activity, have the full phenotype: hyperuricemia, neurologic dysfunction, cognitive deficits, and abnormal behavior including self-injury.

LNV, with some residual HPRT activity, have a partial phenotype: they do not perform self-injurious behavior, they may present with hyperuricemia with varying degrees of motor or cognitive dysfunction, or they may have hyperuricemia alone.[5] LNV are typically subdivided into:

- HPRT-related neurologic disease (HND): hyperuricemia and some degree of neurologic dysfunction and/or cognitive deficits.
- HPRT-related hyperuricemia (HRH): hyperuricemia alone, no neurologic dysfunction.

The eponym Kelley-Seegmiller syndrome has also been applied to LNV.[7] However, this term is best avoided; its definition is unclear because it has variously been used to refer to all variants or only to those with hyperuricemia alone. Moreover, it suggests another disease entity, but it is merely a variant of LND.



Phenotypic spectrum associated with hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. HND: HPRT-related neurologic disease; LND: Lesch-Nyhan disease

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THEORY

Case history

Case history #1

A 2-year-old boy presents with developmental delay and floppiness. Although he is happy and interactive, he is behind in reaching developmental milestones. He rarely turns over, has difficulty holding up his head unsupported for a long time, and is unable to sit independently. He is suspected of having dyskinetic cerebral palsy. When asked, his parents remember sometimes noticing orange "sand" in his diapers in the past. On clinical examination, there is a generalized, severe hypotonia. He displays frequent extraneous movements in his face, neck, and limbs, with twisted and sustained postures that interfere with voluntary movement and are indicative of generalized action dystonia. An MRI of the brain is unremarkable. Metabolic analysis reveals elevated concentrations of uric acid in serum and urine. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) activity is not detectable in cultured fibroblasts. A mutation in the HPRT gene is found.

Case history #2

A 6-year-old boy presents with severe pain in his right flank and lower abdomen, accompanied by nausea. He has also noticed some blood in his urine. His parents report an episode of a red and swollen joint in his left big toe, which was treated with anti-inflammatory agents. Besides severe costovertebral angle tenderness on his right side, a general physical exam is unremarkable. A detailed neurologic exam reveals mild clumsiness and slightly indistinct speech. When performing complicated motor tasks with one hand, the contralateral hand sometimes adopts a mirror posture suggestive of subtle overflow dystonia. Renal ultrasonography confirms nephrolithiasis as the cause of his abdominal pain, and laboratory investigation reveals hyperuricemia. The kidney stone, which passes eventually, shows high urate content. HPRT enzyme activity is 8% of normal.

Approach

Lesch-Nyhan disease (LND) should be considered when delayed development is accompanied by a hyperkinetic disorder, particularly when brain MRI is normal.

It should be suspected if delayed development is accompanied by self-injurious behavior or evidence of excessive production of uric acid. A clinical suspicion should always be confirmed by hypoxanthine-guanine phosphoribosyltransferase (HPRT) molecular gene analysis, and preferably also HPRT enzyme activity.

Virtually all patients are male, owing to the X-linked recessive mode of inheritance. However, a few female patients have been described.[3] A history of LND in other family members might point toward the diagnosis. LND has been reported in most ethnic groups, with approximately equal rates.

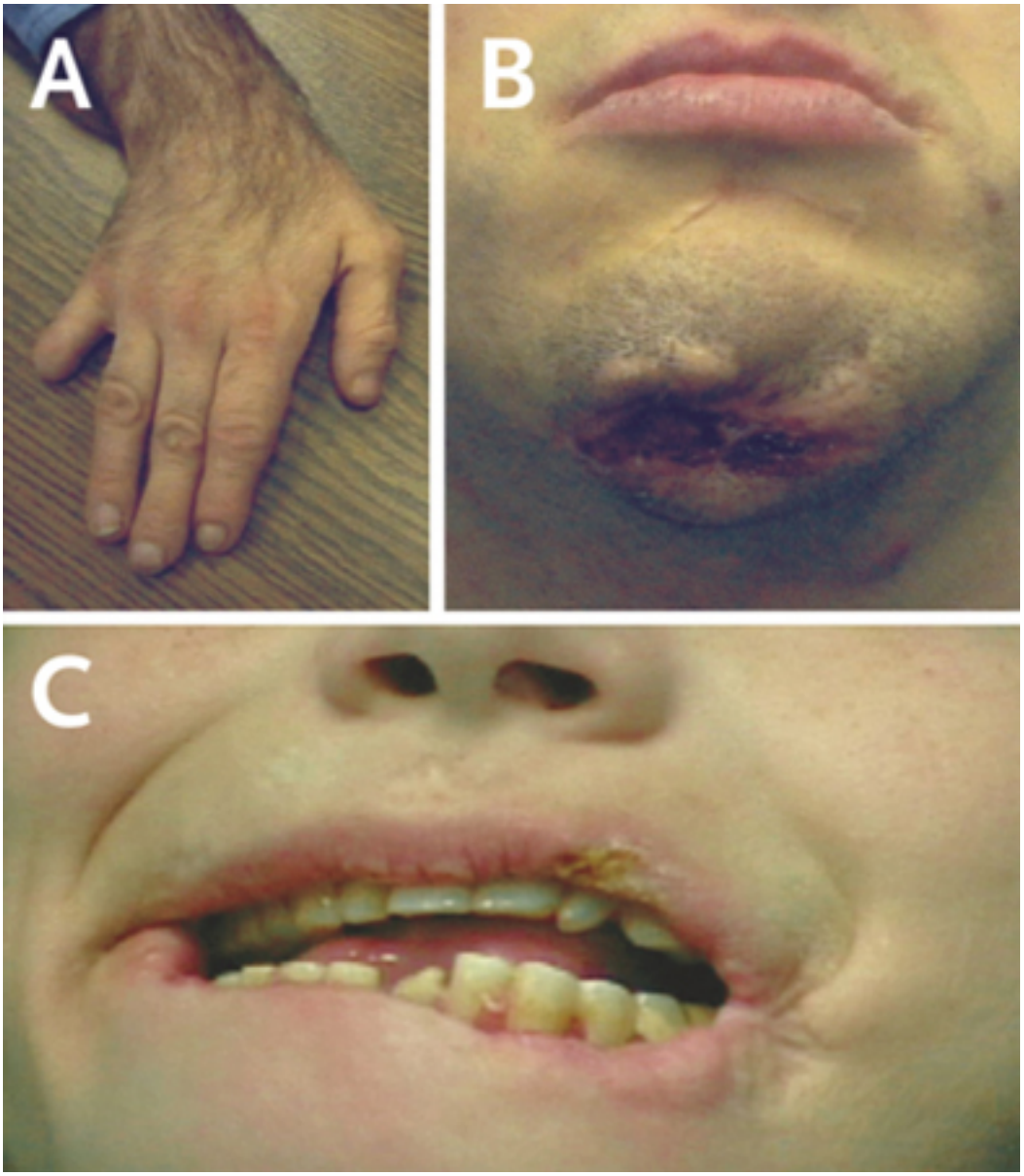
Clinical features

Classic LND patients usually come to clinical attention before the age of 1 year.[22] Most patients come to medical attention early in life, usually before 4 years of age. People with an LN variant (LNV) might present at a later age, depending on the age of onset of renal or neurologic problems.[3]

Typically, self-injurious behavior starts at age 2 to 5 years, although cases of around 18 years of age at onset have been described.[22] Finger and lip biting is a frequently seen form of self-injurious behavior. Subsequent partial amputations of the fingers, lips, tongue, and oral mucosa are common. Such topographic preference is rarely seen in other diseases with self-injury.

Among the most frequent presenting symptoms in classic LND is a failure to reach motor milestones.[22] Sometimes previously achieved motor milestones are lost. Cognitive function is usually impaired, with average intelligence quotient values of approximately 70, although normal intelligence has been described in some patients. Patients do not have global intellectual disability, but rather have impairments in specific cognitive domains involving attention and mental flexibility. Involuntary movements are common among the presenting symptoms, although they may develop later in the course of the disease.[3] A generalized action dystonia is present, characterized by frequent extraneous movements in the face, neck, and limbs, with sustained muscle contractions. This results in twisted postures that interfere with voluntary movement.[3] [22]

On examination, somatic growth is affected more than head circumference or bone age.[23] [24] [25] A generalized hypotonia is frequently seen at presentation.[22] Spasticity and hyperreflexia, implying the involvement of corticospinal pathways, may be present;[3] these features usually appear later in the course of the disease, and are often asymmetrical. The cause is unknown, but they may be a result of myelopathy resulting from forceful involuntary movements of the neck.[3] The presence of orange "sand" crystals in the diaper should be checked or asked about if it is not reported spontaneously. The "sand" and orange color is caused by uric acid crystals and microhematuria.[24] [25] Testicular atrophy is commonly seen, and puberty is often delayed or absent.[23] Undescended testes also occur.[23] [24] [26]



Examples of self-injurious behavior seen in patients with classic Lesch-Nyhan disease

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Hyperuricemia

The majority of LND patients have elevated uric acid levels in serum and urine as a result of HPRT deficiency.[22]Uric acid levels are frequently evaluated as part of the metabolic workup of developmental delay or hypotonia. Urine is best evaluated by 24-hour urinary uric acid-creatinine ratio, or a total 24-hour uric acid excretion.[13] Although high uric acid levels may provide important clues to the diagnosis, they lack sufficient sensitivity and specificity for definitive diagnosis.

The hyperuricemia is also associated with nephrolithiasis, gouty arthritis, and subcutaneous tophi.

Measurement	LND			LNV						Controls	
				HND			HRH				
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Serum uric acid (mg/dL)	11.9	4.4	(88)	13.4	3.6	(28)	12.8	6.3	(35)	4.5	1.3
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Uric acid levels in patients with classic Lesch-Nyhan disease (LND), patients with Lesch-Nyhan variants (LNV), and healthy controls. SD, standard deviation; HRH: hypoxanthine-guanine phosphoribosyltransferase (HPRT)-related hyperuricemia; HRD: HPRT-related neurologic disease

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HPRT enzyme activity

Measurements of HPRT activity in cultured intact cells, such as fibroblasts, are considered more accurate than those in cell lysates.[3] The percentage of residual HPRT activity can provide some predictive value concerning disease severity. The clinical phenotype is a continuum:[27] [28] [29]

- Near complete absence of HPRT activity results in the full phenotype of classic LND
- A residual activity of ≥1.5% usually prevents self-injury and other behavioral disturbances
- Residual activity >8% rarely causes obvious neurologic impairment.

Laboratories where HPRT activity can be measured are listed on the website of the Lesch-Nyhan Disease International Study Group. [Lesch-Nyhan disease international study group] (http://www.lesch-nyhan.org)

HPRT gene analysis

Rapid and reliable tests have been developed to identify HPRT gene mutations using molecular genetic methods. The mutations are heterogeneous, including point mutations and other substitutions, deletions, and insertions.[11] [12] Mutations that predict large aberrations in the resulting protein, such as large deletions or early nonsense mutations, or a mutation identified in a prior patient, appear to be good predictors of disease severity.[11] [12] Point mutations may cause either classic LND or an LNV, depending on the ultimate effect on enzyme activity.

In the US, molecular samples can be sent to Emory Genetics Laboratory. [Emory genetics laboratory] (http://genetics.emory.edu/egl) Other laboratories are listed on the website of the Lesch-Nyhan Disease International Study Group. [Lesch-Nyhan disease international study group] (http://www.lesch-nyhan.org)

Brain imaging

Brain imaging is not normally necessary for diagnosis and management of Lesch-Nyhan disease, but may be helpful if there is clinical suspicion of other diagnoses. Generally, neither CT scanning nor MRI reveal any obvious structural malformations or signal changes.[22] [30] Routine imaging is usually normal, but may reveal mild loss of brain volume.[31]

History and exam

Key diagnostic factors

age <12 months (common)

- Classic Lesch-Nyhan disease (LND) patients usually come to clinical attention before the age of 1 year.[22] People with an LN variant (LNV) might present at a later age, depending on the age of onset of renal problems or neurologic problems.[3]

orange "sand" crystals in diaper (common)

- Should be checked if not reported spontaneously. The "sand" is caused by uric acid crystals and microhematuria.[24] [25]

kidney stones (common)

- If the hyperuricemia and hyperuricosuria is not controlled, there may be a history of nephrolithiasis.[3] [22]

pyramidal signs (common)

- Spasticity and hyperreflexia, implying the involvement of corticospinal pathways, may be present.[3] Usually appears later in the course of the disease, and is often asymmetrical. The cause is unknown, but may be a result of myelopathy resulting from forceful involuntary movements of the neck.[3]

testicular atrophy (common)

- Commonly seen, and puberty is often delayed or absent.[23] Undescended testes also occur.[23] [24] [26]

male sex (common)

- Virtually all patients are male, owing to the X-linked recessive mode of inheritance. However, a few female patients have been described.[3]

developmental delay (common)

- Among the most frequent presenting symptoms in classic LND, presenting as a failure to reach motor milestones.[22] Sometimes previously achieved motor milestones are lost.

involuntary movements (common)

- Usually among the presenting symptoms, but may develop later in the course of the disease.[3]

generalized hypotonia (common)

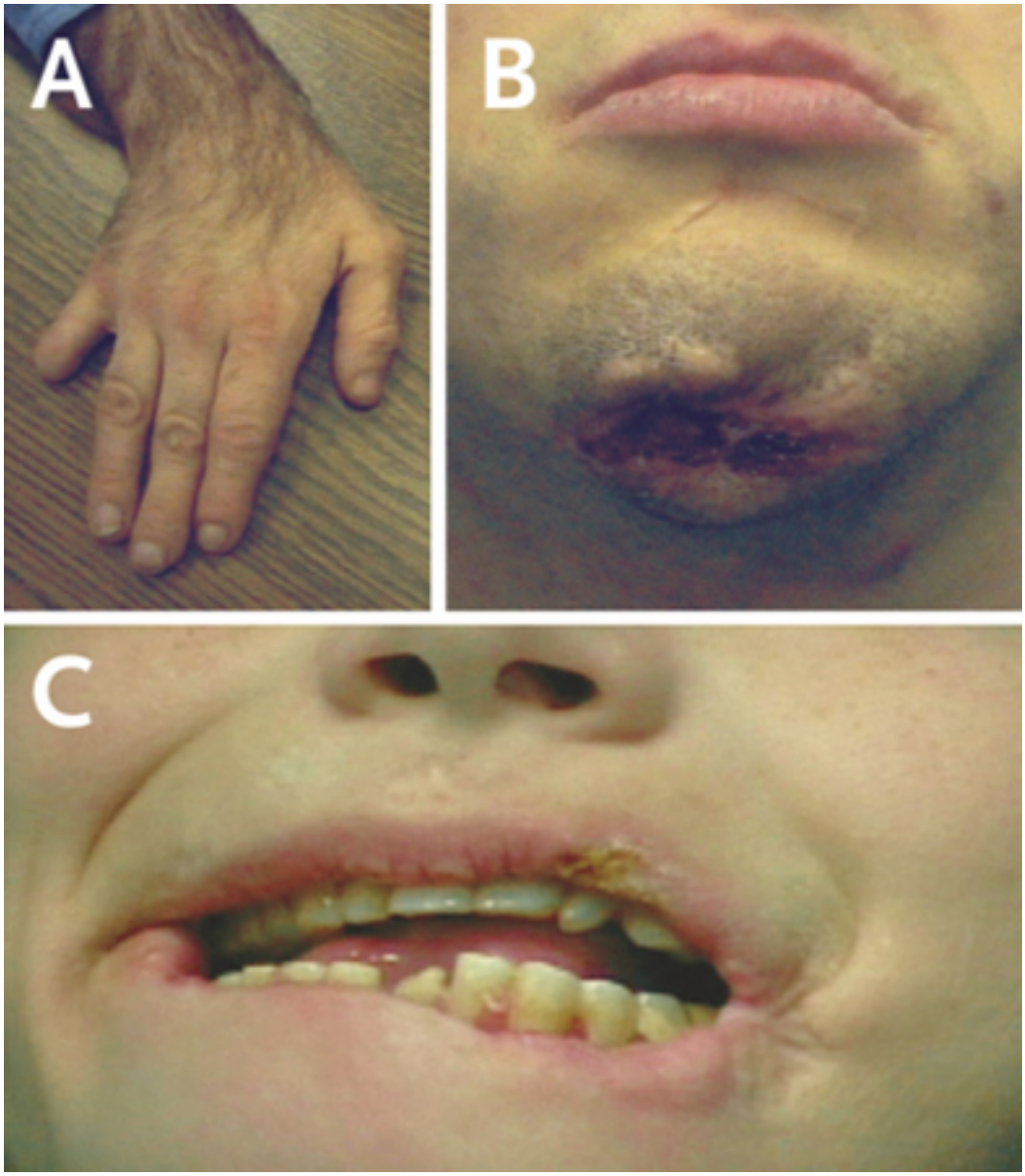
- A generalized hypotonia is frequently seen at presentation, usually in association with developmental delay.[22]

self-injurious behavior, usually at <5 years of age (common)

- Typically, self-injurious behavior starts at age 2 to 5 years, although cases have been described in which it starts about the age of 18 years.[22]

self-injurious behavior focusing on the mouth and fingers (common)

- Finger and lip biting is a frequently seen form of self-injurious behavior. Subsequent partial amputations of the fingers, lips, tongue, and oral mucosa are common. Such topographic preference is rarely seen in other diseases with self-injury.



Examples of self-injurious behavior seen in patients with classic Lesch-Nyhan disease

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cognitive disturbances (common)

- Cognitive function is usually impaired, with average intelligence quotient values of approximately 70, although normal intelligence has been described in some patients. Patients do not have global intellectual disability, but rather have impairments in specific cognitive domains involving attention and mental flexibility.

delayed growth (common)

- Somatic growth is affected more than head circumference or bone age.[23] [24] [25]

action dystonia (common)

- A generalized action dystonia is present, characterized by frequent extraneous movements in the face, neck, and limbs, with sustained muscle contractions. This results in twisted postures that interfere with voluntary movement.[3] [22]

positive family history (uncommon)

- A history of LND in other family members might point toward the diagnosis.

Risk factors

Strong

positive family history

- The absolute risk can be calculated based on the X-linked recessive mode of inheritance. Women may be carriers. Male classic Lesch-Nyhan disease (LND) patients do not usually have children, although it is possible in men with a mild phenotype caused by partial enzyme deficiency.

Investigations

1st test to order

Test	Result
serum uric acid level • Elevated in most patients, but because of rapid renal clearance serum uric acid levels may be normal at the time of testing.[3] [32] May be part of a metabolic workup in patients who present with developmental delay and hypotonia (thus prompting consideration of Lesch-Nyhan disease [LND]).	**elevated**
24-hour urinary uric acid excretion • A spot (or random) urine sample for uric acid is not reliable because uric acid values vary with diet, hydration, and a number of other factors. A 24-hour urinary uric acid level is, therefore, more reliable, especially if it is normalized to body mass by determining the uric acid-creatinine ratio. However, complete 24-hour specimens are notoriously hard to collect, especially in children.	**elevated**
hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene analysis • Usually performed after measurement of uric acid levels, and often combined with HPRT enzyme activity, but may be the first test ordered in cases of high clinical suspicion or known HPRT mutation in the family. Mutations might provide clues about disease severity.	**mutation in the coding region of the HPRT gene**
HPRT enzyme activity • HPRT activities in cultured live cells (fibroblasts) are considered more reliable than those in cell lysates, owing to possible kinetic and stability properties of mutant HPRT enzyme.[3]	**reduced; typical values (% of normal): classic LND <1.5%; hyperuricemia with neurologic dysfunction (HRND) <8%; HPRT-related hyperuricemia (HRH) ≥8%**

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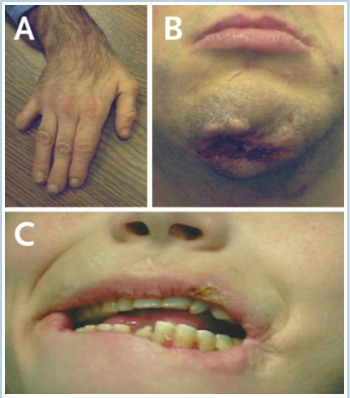
Other tests to consider

Test	Result
brain MRI • Brain imaging is not normally necessary for diagnosis and management of Lesch-Nyhan disease, but may be helpful if there is clinical suspicion of other diagnoses. • Generally, neither CT scanning nor MRI reveals any obvious structural malformations or signal changes.[22] [30]Routine imaging is usually normal, but may reveal mild loss of brain volume.[31]	**may reveal mild loss of brain volume**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Cerebral palsy	• Owing to the occurrence of hypotonia and developmental delay early in the course of the disease, many patients are diagnosed as having cerebral palsy until the telltale features of Lesch-Nyhan disease (LND), such as self-injury or overproduction of uric acid, are recognized.	• Hyperuricemia is not typical in cerebral palsy. • Hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene analysis and HPRT enzyme activity will provide definite diagnosis in cases of LND.
Diseases with developmental delay	• The differential diagnosis for developmental delay is extensive.[33] • LND should be suspected if delayed development is accompanied by self-injurious behavior or evidence of excessive production of uric acid.	• Hyperuricemia is not typical in these conditions. • HPRT gene analysis and HPRT enzyme activity will provide definite diagnosis in cases of LND.
Diseases with dystonia at young age	• The differential diagnosis for dystonia at young age is extensive.[34] • LND should be suspected if dystonia is accompanied by self-injurious behavior or evidence of excessive production of uric acid.	• Hyperuricemia is not typical in these conditions. • HPRT gene analysis and HPRT enzyme activity will provide definite diagnosis in cases of LND.
Other diseases with self-injury (e.g., intellectual disability, autism, Prader-Willi syndrome, fragile X syndrome)	• Self-injury in LND is usually more severe than in other conditions, and the prominent topographic preference for mouth and fingers is not frequently seen in other conditions.[35] • Self-injurious behavior in LND is always accompanied by profound motor impairment. LND should be suspected when self-injurious behavior is associated with the typical motor dysfunction emerging early in life, especially if there is also hyperuricemia.	• Hyperuricemia is not typical in these conditions. • HPRT gene analysis and HPRT enzyme activity will provide definite diagnosis in cases of LND.

Condition	Differentiating signs / symptoms	Differentiating tests
	 *Examples of self-injurious behavior seen in patients with classic Lesch-Nyhan disease* *From the collection of H.A. Jinnah, MD, PhD; used with permission*	

Screening

Carrier testing

Carrier testing of women who give birth to a child with Lesch-Nyhan disease (LND) should be performed, as well as genetic counseling, to determine the risk of having more affected children. Other female family members could also be screened to determine their risk. This is most conveniently and adequately performed by molecular techniques (i.e., genetic testing), particularly if a mutation has been characterized in the affected LND patient.[36] Mothers of affected boys are not necessarily obligate carriers because of possible de novo mutation during gametogenesis or early development. Even after negative screening results for the mother, subsequent pregnancies should be monitored because the risk of gonadal mosaicism.[36] The use of hypoxanthine-guanine phosphoribosyltransferase (HPRT) activity levels as a screening instrument is insufficiently accurate.[3]

Prenatal testing

All pregnancies of a carrier should be monitored if termination of affected pregnancies is being considered. Genetic testing for a mutation in the HPRT gene in amniotic fluid or chorionic villus samples provides the earliest opportunity and most accurate means for deciding on a therapeutic abortion if this is desired.[36] Measuring HPRT activity in amniotic fluid or chorionic villus samples is not recommended, because it can only be performed at least 2 months after conception and is subject to sampling error.[3]

Approach

Currently, there is no curative treatment for Lesch-Nyhan disease (LND). Supportive treatment options depend on the phenotype, which includes overproduction of uric acid and its complications, as well as varying degrees of extrapyramidal and pyramidal signs, behavioral abnormalities including self-injurious behavior, and miscellaneous aspects such as macrocytic anemia.

Hyperuricemia

All patients have hyperuricemia. Allopurinol inhibits the conversion of xanthine and hypoxanthine to uric acid, and so reduces the risk of hyperuricemia-associated urologic and articular complications by effectively reducing serum acid levels.[37] [38] Doses are titrated to maintain uric acid levels in the high-normal range and must be adjusted for renal insufficiency. In addition, generous hydration at all times is essential to wash out the oxypurines hypoxanthine and xanthine, and the allopurinol metabolite oxypurinol, which may also cause (radiolucent) renal stones.[39] [40]

Renal stones

Renal stones, identified by renal colic, urinary obstruction, or routine ultrasound follow-up, require appropriate treatment in order to prevent long-term renal complications.[40] [41] Kidney stones in allopurinol-treated LND patients may contain uric acid, the oxypurines xanthine and hypoxanthine, or the allopurinol metabolite oxypurinol.[39] These stones are radiolucent, so renal ultrasound is the preferred modality for diagnosis.[40] Small urate stones can usually be managed by increasing fluid intake and by urine alkalinization, with potassium citrate being the preferred agent. Large stones and oxypurine stones may require lithotripsy or surgery, although the latter are more difficult to eliminate.[39] [41]

Dystonia, chorea and ballismus

Extrapyramidal features in LND are mostly resistant to currently available therapies.

Various drug therapies have been tried. Dopaminergic drugs such as levodopa have inconsistent effects on the motor disorder and have been reported to worsen the condition.[21] [26] [42] Early treatment with levodopa/carbidopa (i.e., starting <1 year after the onset of symptoms) has been reported to improve the movement disorder in one patient but confirmative studies are warranted.[43] Symptomatic treatment of severe dystonia (e.g., to improve hand function or prevent contractures) can be performed by botulinum toxin injections in selected muscles. Choreiform and ballistic movements do not consistently improve with a dopamine receptor antagonist (e.g., fluphenazine, pimozide) or drugs that deplete dopamine stores (tetrabenazine).[26] [42] [44] [45] Detailed reports on the use of trihexyphenidyl in LND are lacking.

Physical therapy is generally useful to prevent contractures and preserve overall physical condition.

Pyramidal signs

Muscle relaxants such as baclofen and dantrolene can be used to manage spasticity.[3]

Alternatively, benzodiazepines (e.g., diazepam) may be used. Benzodiazepines have the added advantage of reducing anxiety, which is known to exacerbate the extrapyramidal and behavioral features.

Often, a muscle relaxant and a benzodiazepine are used concurrently.

In addition, physical therapy may prevent contractures and preserve overall condition.

Behavioral abnormalities

No pharmacologic treatment has consistently demonstrated effectiveness in managing the behavioral disturbances in LND, including medications that influence dopamine and serotonin metabolism.[26] [44] [45] [46] No pharmacologic treatment has been reported as consistently reducing self-injurious behavior.[3] A positive effect of S-adenosylmethionine on behavior has not been established, as results are inconsistent.[47] Behavioral abnormalities do not respond consistently to formal psychological treatment either.[3] Negative reinforcement usually increases unwanted behaviors, including self-injury.[48] [49]

The most effective method of dealing with difficult behaviors is to acknowledge the fact that they are beyond the patient's control, engage the patient in an active environment, provide positive reinforcement for desired behaviors, and actively ignore undesirable behaviors. For many patients, it is of utmost importance that they feel understood.

Most LND patients need some form of physical restraint, such as arm splints, limb straps, or protective gloves.[3] [50] [51] For biting, teeth extraction may be needed when conservative measures fail.[52] Hard objects that can be reached, including wheelchairs, need soft padding.[53]

During inpatient admissions, limited to those that are absolutely necessary, restraints should be applied at all times to prevent self-injury, including during sleep. This disease is exempted from the regulations of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) against continuous and long-term restraints.

Macrocytic anemia

Macrocytic anemia may be found in LND patients.[26] [54] The cause is uncertain, as serum vitamin B12, folate, iron, and thyroid function tests are typically normal, and supplements are usually not effective.[3]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
all patients		
	1st	allopurinol
	plus	generous hydration
	plus	physical therapy to reduce contractures
with dystonia, chorea, and/or ballismus	adjunct	botulinum toxin injection
with spasticity	adjunct	muscle relaxant and/or benzodiazepine
with behavioral abnormalities	plus	positive reinforcement for desired behaviors
	adjunct	measures to counter self-injurious behavior
with renal stones	plus	increased fluid intake and urine alkalinization
	adjunct	lithotripsy or surgery

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

all patients

1st **allopurinol**

Primary options

» allopurinol: children: 10 mg/kg/day orally given in 2-3 divided doses, titrated to maintain uric acid levels in the high-normal range, maximum 800 mg/day; adults: 100-600 mg/day orally given in 2-3 divided doses, titrated to maintain uric acid levels in the high-normal range, maximum 800 mg/day

» Allopurinol reduces the risk of hyperuricemia-associated urologic and articular complications by effectively reducing serum acid levels.[37] [38] Allopurinol inhibits the conversion of xanthine and hypoxanthine to uric acid.

» Doses are titrated to maintain uric acid levels in the high-normal range and must be adjusted for renal insufficiency.

plus **generous hydration**

Treatment recommended for ALL patients in selected patient group

» In addition to allopurinol, generous hydration at all times is essential to wash out the oxypurines hypoxanthine and xanthine, and the allopurinol metabolite oxypurinol, which may also cause (radiolucent) renal stones.[39] [40]

» Generally, the suggestion is a total fluid intake of 2 to 2.5 L per 1.73 m^2 body surface area (BSA). In adults, a target urinary volume of at least 1.5 L, preferably 2 to 2.5 L, has been advocated. The goal is to lower uric acid concentration in the urine and also to avoid dehydration during episodes of fever or vomiting (e.g., on hot days).

plus **physical therapy to reduce contractures**

Treatment recommended for ALL patients in selected patient group

» Physical therapy is generally useful to prevent contractures and preserve overall physical condition.

with dystonia, chorea, and/or ballismus **adjunct** **botulinum toxin injection**

MANAGEMENT

Ongoing

Treatment recommended for SOME patients in selected patient group

Primary options

» onabotulinumtoxinA: consult specialist for guidance on dose

» Symptomatic treatment of severe dystonia (i.e., to improve hand function or prevent contractures) can be performed by botulinum toxin injections in selected muscles.

» The dose depends on the severity of the dystonia, the muscle being injected, and the preferences of the doctor.

with spasticity — **adjunct** — **muscle relaxant and/or benzodiazepine**

Treatment recommended for SOME patients in selected patient group

Primary options

» baclofen: children: consult specialist for guidance on dose; adults: 5 mg orally three times daily initially, titrate according to response, maximum 70 mg/day
-or-

OR

» dantrolene: children: 1 mg/kg/day orally given in 3-4 divided doses, titrate according to response, maximum 400 mg/day; adults: 25 mg/day orally initially given in divided doses, titrate according to response, maximum 400 mg/day
--AND/OR--

OR

» diazepam: children: 0.12 to 0.8 mg/kg/day orally given in 3-4 divided doses; adults: 2-10 mg orally three to four times daily

» A muscle relaxant such as baclofen or dantrolene can be used if spasticity is a problem.[3]

» Often, a muscle relaxant and a benzodiazepine are used concurrently. Benzodiazepines have the additional advantage of reducing anxiety, which is known to exacerbate the extrapyramidal and behavioral features

with behavioral abnormalities — **plus** — **positive reinforcement for desired behaviors**

Ongoing

Treatment recommended for ALL patients in selected patient group

» The most effective method to deal with difficult behaviors is to acknowledge the fact that they are beyond the patient's control, engage the patient in an active environment, provide positive reinforcement for desired behaviors, and actively ignore undesirable behaviors. For many patients, it is of utmost importance that they feel understood.

» No pharmacologic treatment has consistently demonstrated effectiveness in managing behavioral disturbances in Lesch-Nyhan disease (LND); they do not respond consistently to formal psychological treatment either.[3] Negative reinforcement usually increases unwanted behaviors.[48] [49]

adjunct **measures to counter self-injurious behavior**

Treatment recommended for SOME patients in selected patient group

» Self-injury is best managed by engaging the patient in an active environment and actively ignoring the self-injurious behavior. Negative reinforcement might increase self-injury.[48] [49]

» Most patients need some form of physical restraint such as arm splints, limb straps, or protective gloves.[3] [50] [51] Teeth extraction is needed to counter biting when conservative measures fail.[52] Hard objects that can be reached, including wheelchairs, need soft padding.[53]

with renal stones **plus** **increased fluid intake and urine alkalinization**

Treatment recommended for ALL patients in selected patient group

Primary options

» potassium citrate: see local protocol for administration guidelines

» Small urate stones can usually be managed by further increasing fluid intake and by urine alkalinization, with potassium citrate being the preferred agent. Treatment is required to prevent long-term renal complications.[40] [41]

adjunct **lithotripsy or surgery**

Treatment recommended for SOME patients in selected patient group

MANAGEMENT

Ongoing

» Large stones and oxypurine stones may require lithotripsy or surgery, although the latter are more difficult to eliminate.[39] [41] Treatment is required to prevent long-term renal complications.[40] [41]

Emerging

Deep brain stimulation (DBS)

In DBS, high-frequency electrical stimulation is applied via an electrode to specific brain areas, where it inhibits neuronal activity in overactive regions. To date, several Lesch-Nyhan disease (LND) patients who have received DBS, targeted at the globus pallidus pars interna, have been reported in the literature.[55] [56] [57] [58] [59] [60] [61] [62]Some showed remarkable improvements in motor dysfunction, and even self-injury, but these may not be sustained, and complications have frequently been noted.[63] More studies are needed before DBS can be considered effective and safe in LND.

Selective dopamine receptor antagonists

A trial of the selective dopamine D1/D5 receptor antagonist ecopipam in LND patients was terminated early due to unanticipated side effects.[64] However, because the drug appeared to reduce self-injury in most of the limited number of patients enrolled, ecopipam could be a useful treatment for self-injurious behavior in LND. Further studies are warranted before it can be considered effective and safe in LND.

Primary prevention

Because there are currently no effective therapies available for the neurobehavioral features of Lesch-Nyhan disease (LND), primary prevention is the most important medical intervention. This includes genetic counseling for families with LND patients and determining the carrier status of women in these families. Female carriers should have all subsequent pregnancies monitored with preimplantation, or prenatal diagnosis if the family would consider termination in the case of an affected pregnancy. Appropriate guidance regarding family planning should be provided.

Patient discussions

Patients should have uric acid levels monitored regularly, at least once a year after a stable dose of allopurinol has been achieved, and have regular renal ultrasound evaluations (e.g., once a year). Regular follow-up appointments, preferably with clinicians experienced in this disease, can help to identify and treat further neurologic and orthopedic complications early.

FOLLOW UP

Monitoring

Monitoring

Nephrologic follow-up includes serum uric acid measurements, in order to enable proper adjustment of allopurinol doses. Yearly ultrasound evaluations have been recommended for detection and treatment of subclinical nephrolithiasis, to prevent long-term renal complications.[41]

Rehabilitation doctors might monitor special-care needs such as specialized wheelchairs and communication devices. Regular follow-up visits to a neurologist (preferably one experienced in the management of Lesch-Nyhan disease [LND] and its variants) is recommended in order to educate the patient and family members. Refer to appropriate specialists if needed (e.g., special-care dentists for teeth extraction, orthopedic surgeons in case of hip dislocations or scoliosis).

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
contractures	**long term**	**high**
If dystonia and spasticity are present, contractures are likely to occur. Contractures can be prevented by optimizing pharmacologic treatment and by physical therapy.		
kidney stones	**variable**	**high**
Allopurinol and generous fluid intake are key to controlling hyperuricemia and preventing nephrolithiasis. However, persistent nephrolithiasis may still occur, possibly leading to renal failure.		
gouty arthritis	**variable**	**high**
If hyperuricemia persists, arthritis may occur as a result of the formation of uric acid crystals in synovial fluid. This can be prevented by carefully controlling the hyperuricemia.		
urinary infections	**variable**	**high**
Persistent nephrolithiasis may lead to urinary infections and urosepsis. Adequate treatment with allopurinol and generous fluid intake are mandatory, and preventive antibiotics are sometimes helpful.		
skin and soft tissue infections	**variable**	**medium**
Skin abrasions and soft tissue defects may occur as a result of self-injurious behavior. Subsequently, wound infections may occur.		
hip dysplasia and subluxation or luxation	**variable**	**medium**
Hip dysplasia may occur in Lesch-Nyhan disease (LND), presumably caused by muscle imbalance. Hip subluxation and luxation, sometimes caused by self-injurious behavior, may require surgical intervention.[66]		
other orthopedic complications	**variable**	**medium**
Scoliosis, fractures, and atlanto-axial subluxation have been reported in LND, caused by severe dystonia and self-injurious behavior.[66] [67]		
pneumonia	**variable**	**low**
Patients might experience progressive dysphagia and die after aspiration and pneumonia. Percutaneous endoscopic gastrostomy (PEG) should be considered in patients with frequent choking or insufficient intake.		

Prognosis

Course

Lesch-Nyhan disease (LND) patients do not usually develop the ability to walk or sit unsupported.[22] They need help with activities of daily living, such as eating, drinking, and personal hygiene. The hyperkinetic movement disorder is usually considered stable after a few years of age, but pyramidal signs might increase during life. Functional abilities might further decrease as a result of contractures if these cannot be fully prevented.

Life span

Few people with LND live beyond 40 years of age, though patients with mildly affected variants may have a normal lifespan.[3] Despite the use of allopurinol to control hyperuricemia, renal failure or urosepsis may occur, owing to persistent nephrolithiasis. Some patients experience progressive dysphagia, and may die after pneumonia caused by aspiration. Sudden unexpected death is relatively common. When sudden death does occur, respiratory failure from cervical pathology or laryngospasm may be responsible.[65]

Online resources

1. GeneReviews: Lesch-Nyhan syndrome (http://www.ncbi.nlm.nih.gov/books/NBK1149) *(external link)*
2. Lesch-Nyhan disease international study group (http://www.lesch-nyhan.org) *(external link)*
3. Emory genetics laboratory (http://genetics.emory.edu/egl) *(external link)*

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Images

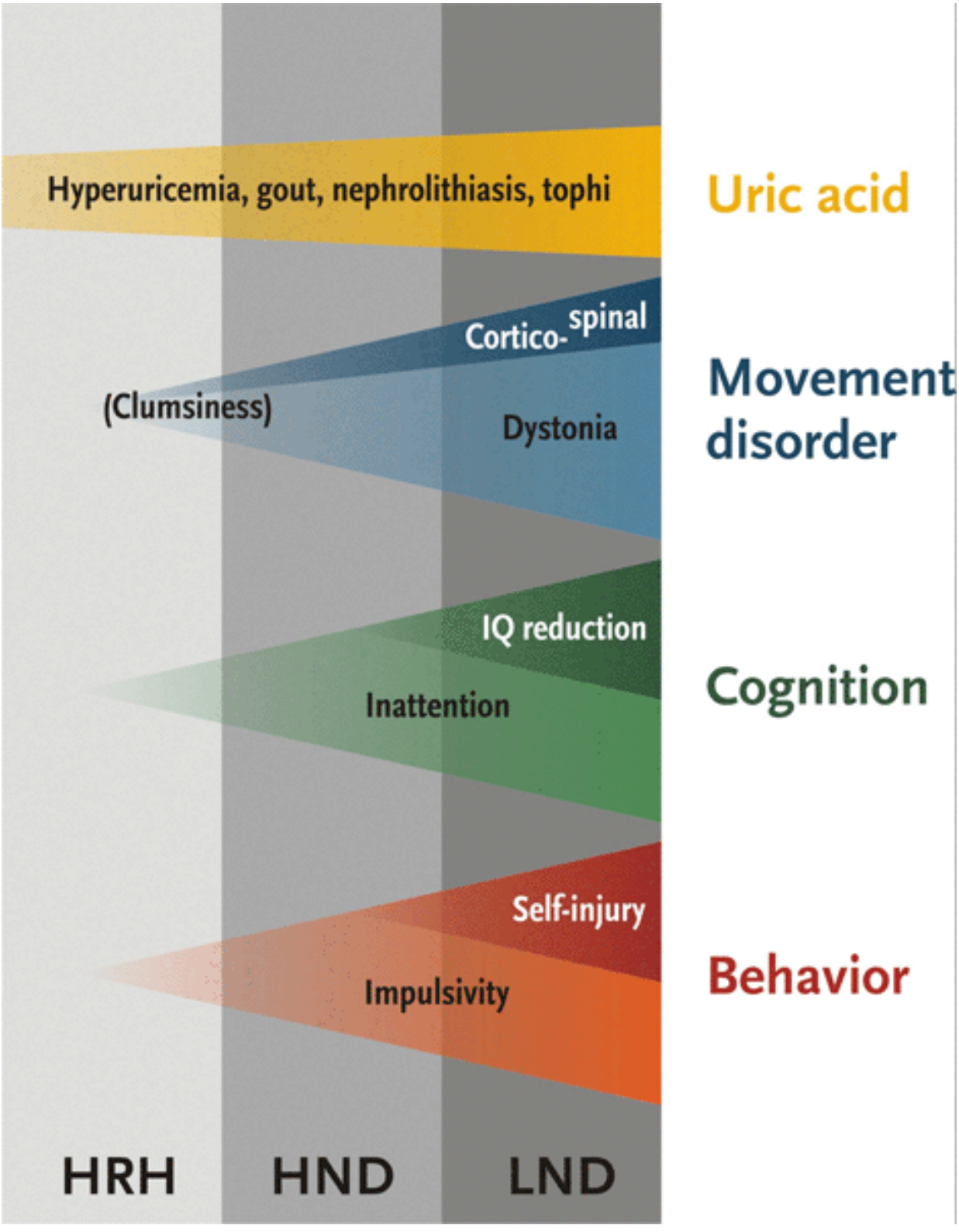

Figure 1: Phenotypic spectrum associated with hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. HND: HPRT-related neurologic disease; LND: Lesch-Nyhan disease

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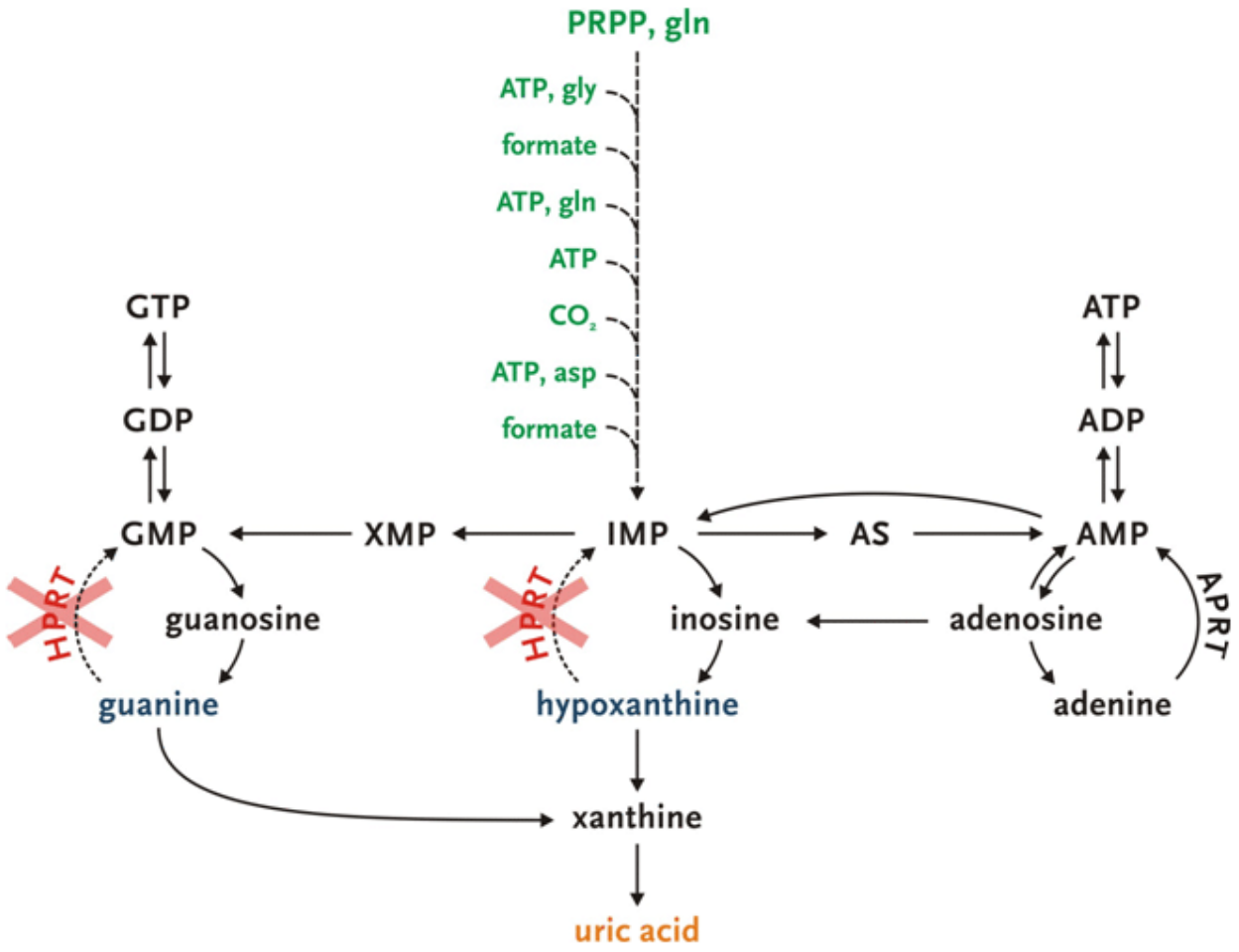

Figure 2: The role of hypoxanthine-guanine phosphoribosyltransferase (HPRT) in the grand scheme of purine metabolism

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Measurement	LND			LNV						Controls	
				HND			HRH				
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Serum uric acid (mg/dL)	11.9	4.4	(88)	13.4	3.6	(28)	12.8	6.3	(35)	4.5	1.3
Urine uric acid/creatinine ratio	2.9	1.1	(18)	1.6	1.3	(5)	1.0	0.5	(24)	0.3	0.1
Urine uric acid excretion (mg/kg/day)	39.6	13.4	(27)	33.6	17.6	(8)	23.5	10.3	(10)	9.7	3.7

Figure 3: Uric acid levels in patients with classic Lesch-Nyhan disease (LND), patients with Lesch-Nyhan variants (LNV), and healthy controls. SD, standard deviation; HRH: hypoxanthine-guanine phosphoribosyltransferase (HPRT)-related hyperuricemia; HRD: HPRT-related neurologic disease

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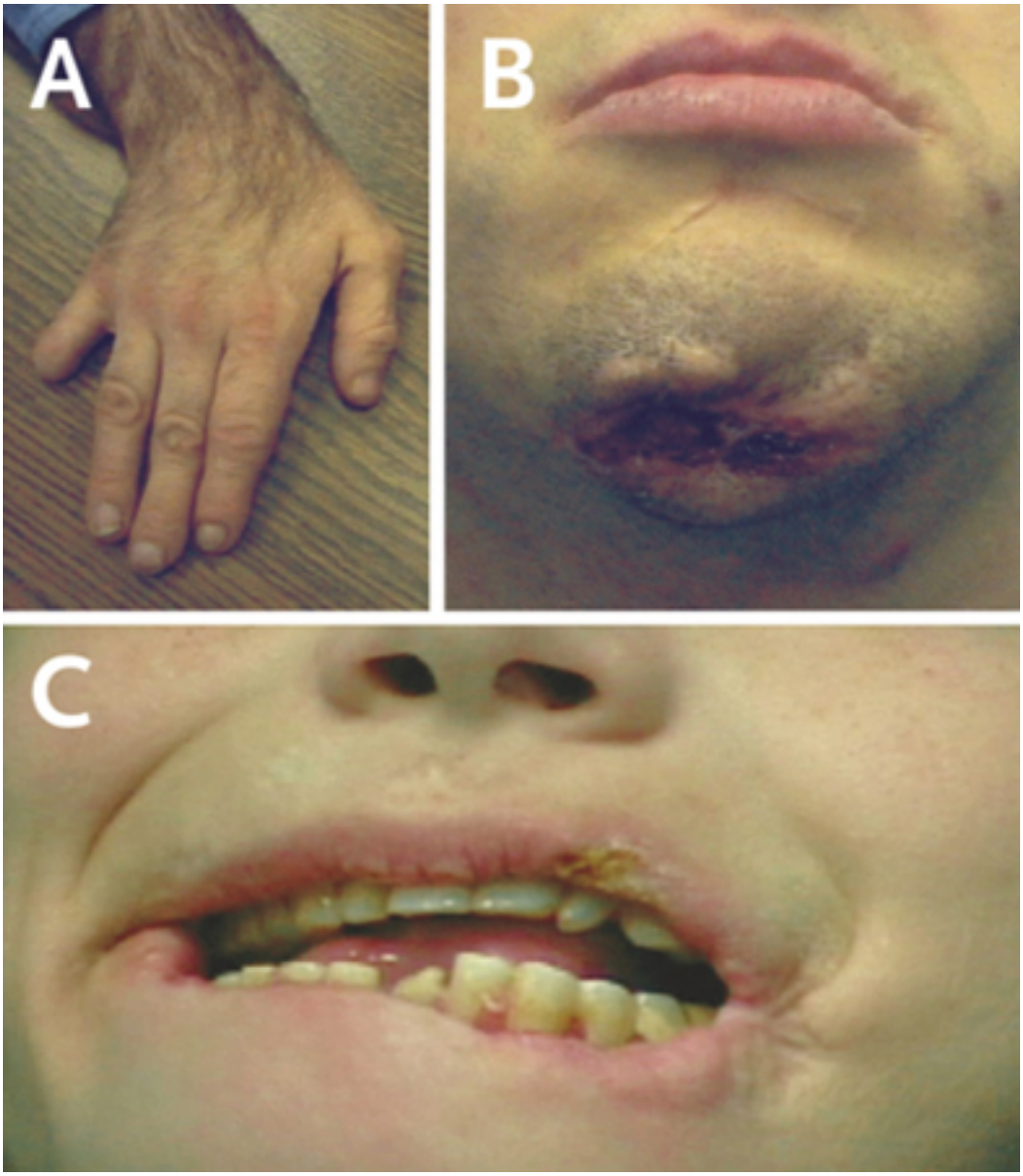

Figure 4: Examples of self-injurious behavior seen in patients with classic Lesch-Nyhan disease

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Figure 1 – BMJ Best Practice Numeral Style

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