

## Understanding Lesch-Nyhan Disease: A Personal Perspective

Stephanie Wincik, RN, CDDN  
and  
William Melius

## What is Lesch-Nyhan Disease?

- An inherited X-linked recessive genetic disorder
- Identified by Michael Lesch and William Nyhan in 1964, although descriptions exist dating back to the 13<sup>th</sup> century
- Occurs almost exclusively in males
- Prevalence is approximately 1 in 380,000
- Caused by a mutation in the HPRT1 gene

## Role of purine metabolism in LND

- In LND, enzyme HPRT is absent or deficient
- Purine is not broken down properly due to the absence of HPRT
- The purine metabolism error results in overproduction of uric acid
- Sodium urate crystals accumulate in the joints, kidneys, CNS, and other tissues

## Signs and Symptoms

- Dystonia
- Abnormal involuntary muscle movements
- Joint pain, gouty arthritis
- Impaired renal function, including kidney and bladder stones
- Extrapyramidal features
- Self-mutilating behaviors

## Signs and Symptoms, cont'd

- Cognitive impairment may be present but is usually mild
- Unintelligible speech and difficulty ambulating are common due to uncontrollable muscle movements

## Diagnosis

- Delayed motor development noticed at 3-12 months
- Abnormal involuntary movements at 6-18 months; may receive diagnosis of CP
- Emergence of self-injurious behavior (SIB) may begin as early as age 2 or as late as age 12
- SIB is often the essential clue that leads to definitive diagnosis

### Diagnosis, cont'd

- Infrequently, first sign is hematuria or renal insufficiency
- Parents often report the appearance of "orange sand" in diapers, caused by uric acid crystals
- Serum uric acid levels not reliable for diagnostic purposes as hyperuricemia may have many different causes

### Diagnosis, cont'd

- CT and MRI usually normal
- PET scans have shown abnormality in the area of the basal ganglia—not fully understood
- Definitive diagnosis is obtained by measurement of HPRT enzyme activity in blood or tissue
- Confirmed by identifying a molecular genetic mutation in the HPRT gene

### Variants of LND

- LND occurs in varying degrees; may be classic or partial
- If the gene mutation is not located in the "classic" position, more enzyme activity may be present, resulting in less severe symptoms and behaviors
- In partial variants, dystonia may be mild or absent and self-injury may not occur

### Prognosis

- Life expectancy varies; average age of death is early to mid-twenties
- With optimal medical care, many individuals with LND survive well into their 40's and 50's
- Chief causes of death are renal failure and aspiration pneumonia
- Sudden unexpected death is common for unknown reasons; respiratory failure secondary to laryngospasm has been suggested

### LND as a Behavioral Phenotype

- A behavioral phenotype is the external expression of a set of genes
- LND is one of the best examples of a behavioral phenotype
- Only individuals with the affected gene display the behaviors unique to LND and vice versa, therefore information about either the gene or the behavior can be used to diagnose LND

### Behavioral Manifestations

- The first self-injurious behavior to be observed is often lip biting
- Behaviors tend to follow a pattern that is consistent throughout the lifespan
- Behaviors may be self-directed or directed toward others
- Both physical and emotional self-injury occurs

### Behaviors, cont'd

Other behaviors include:

- Finger biting
- Chewing of the oral cavity
- Eye-poking
- Placing fingers in wheelchair spokes
- Extending arms in doorways
- Head banging
- Falls
- Self-induced vomiting

### Behaviors, cont'd

Aggressive physical behaviors directed toward others:

- Spitting
- Hitting
- Kicking
- Biting
- Head-butting

### Non-physical behaviors

- Individuals with LND also display behaviors which cause emotional self-injury
- These behaviors are often directed toward caretakers and family members, but may also be directed toward strangers in a public setting
- May target "favorite" caregivers or family members

### Non-physical behaviors, cont'd

Emotional self-injurious behaviors include:

- Swearing
- Racial or ethnic slurs
- Inappropriate sexual comments
- Lying
- Frequently changing opinions

### Counterproductive Behaviors

- Individuals with LND commonly exhibit behaviors that seem contrary to their own best interests
- May refuse to participate in a preferred outing or favorite activity
- May deliberately provide incorrect test answers
- May attempt to alienate others with insulting remarks

### Positive Traits

- Is remorseful after physically injuring or hurting someone's feelings
- Extremely sociable
- Excellent sense of humor
- Observant
- Caring
- Interested in the activities and feelings of others

## Treatment

- Effective treatment for LND must include a combination of:
- Uric acid control
- Maintenance of optimal renal function
- Management of SIB
- Adaptive equipment/Protective devices
- Psychological support
- Dysphagia management

## Uric Acid Control

- Allopurinol is effective in reducing the overproduction of uric acid
- Dose is titrated to maintain uric acid within the normal range of 2.5-8.0mg/dL
- Average adult dose is 300mg daily
- Avoid temptation to suppress uric acid levels below the normal range—more is not better, and may lead to the development of oxypurine stones

## Maintenance of Optimal Renal Function

- Minimum of 40 ounces (1,200 ml) fluid daily, preferably water. May increase to 2,000ml daily if tolerated. Increase intake in hot weather.
- Quarterly BUN, electrolytes, serum creatinine
- Matheny School recommends urinalysis 3xweek—if specific gravity is >1.020 or pH is <6.5 or >7.5 over several readings, fluid intake and acid/base balance is adjusted.

## Maintenance of Optimal Renal Function, cont'd

- Frequent urinalysis may not be feasible for incontinent individuals. If so, consistent adequate fluid intake is key.
- Kidney stones very common in LND; asymptomatic stones can silently compromise renal function
- Yearly renal ultrasound to monitor for stones
- Yearly 24 hour urine for creatinine clearance

## Management of SIB

- To date, no medication has been found to be consistently effective in controlling the SIB of LND
- Anecdotal reports from parents indicate that certain anticonvulsants and antipsychotics are sometimes helpful:

Tegretol	Neurontin	Mellaril
Dilantin	Risperdal	Haldol

## Management of SIB, cont'd

- In most cases, the positive effect from these medications has been transient
- Baclofen is often helpful in reducing spastic movements
- Valium has shown effectiveness as a muscle relaxant, and for reducing stress and anxiety in some individuals

### Management of SIB, cont'd

- Best results are achieved with a combination of medication and behavior modification techniques
- It is essential for all direct care and other support staff to fully understand LND, the expected behaviors, and the treatment plan before working with the individual
- Caregivers must understand that the behaviors are not deliberate

### Management of SIB, cont'd

- Behaviors are often triggered by stressors such as physical discomfort, unfamiliar caregivers, or anxiety surrounding personal care
- Bathing, dressing, toileting, and transferring are extremely stressful due to fear of self-injury when protective devices are removed
- Continuity of caretakers often results in fewer behaviors as the individual is less anxious

### Management of SIB, cont'd

- Consistent ignoring of behaviors is essential for a successful treatment plan
- Reacting to behaviors causes escalation
- Ignoring is often very difficult for caregivers, especially when unprepared
- Occasionally behaviors *are* deliberate—often hard to tell the difference—parents and familiar caregivers have the most success

### Adaptive Equipment Protective Devices

- Individuals with LND are terrified of self-injury
- SIB are uncontrollable and painful
- Individuals are very creative in finding new ways to self-injure—caregivers must be equally inventive in finding solutions that provide protection and help the individual feel secure

### Adaptive/Protective, cont'd

- SIB in LND has a physiological basis, therefore protective devices are necessary and are not considered restraints in the classic sense
- Use of protective devices greatly reduces anxiety and increases feelings of control
- Individuals often participate in the choice of device and decide when to apply and remove

### Adaptive/Protective, cont'd

- Devices and equipment are highly individualized, but may include:
- Custom wheelchair with seatbelt, chest vest, and headrest
- Sandbags for bedtime positioning
- Sleep sack
- Arm guards
- Helmet
- Protective eyewear

## Psychological Support

- Individuals with LND are acutely aware of their situation and often express frustration and feelings of loss
- Depression is common
- Individuals should be evaluated routinely by a psychologist and psychiatrist
- Counseling and antidepressant medication is often necessary

## Dysphagia Management

- Decreased esophageal motility is common
- Aging tends to exacerbate swallowing difficulties
- Modified barium swallow should be completed periodically to monitor dysphagia; diet level adjustments may be required
- Some individuals may require gastrostomy if aspiration becomes a problem

## Teeth Extraction

- Approximately 60% of individuals with LND have undergone full dental extractions to prevent tissue damage from biting lips, tongue, and fingers
- Individuals with LND request the procedure and express enormous relief afterward
- Mouth guards are effective for about 20% of individuals, for others they become a potential source of self-injury

## Experimental Therapies

- Deep brain stimulation surgery appears promising for control of abnormal movements and behaviors .
- More study is needed—the brain targets appear different from those seen in Parkinson's disease and other movement disorders

## Experimental Therapies, cont'd

- Emory University is currently studying the effects of Ecopipam, a dopamine antagonist, which may be helpful in reducing behaviors and abnormal movements in LND. More clinical trials are needed before this drug can be recommended.

## Helpful Websites

- Lesch-Nyhan Disease Support Group  
[www.lndnet.ning.com](http://www.lndnet.ning.com)
- Lesch-Nyhan Disease International Study Group  
[www.lesch-nyhan.org](http://www.lesch-nyhan.org)

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