Lesch-Nyhan Syndrome

MARY ET BOYLE, PH. D.
DEPARTMENT OF COGNITIVE SCIENCE, UCSD
Dr. William Nyhan's young patients have slugged him, kicked him and thrown his eyeglasses across the room. But they mean him no harm: Defective genes rob them of control over their bodies, causing them to chew on themselves and hurt others.
Lesch-Nyhan Disease

WILLIAM L. NYHAN

Department of Pediatrics, University of California San Diego La Jolla, CA, USA

The first description of Lesch-Nyhan disease was in 1964; the first two patients were seen in 1963. The disease has caught the imagination of a variety of clinicians and scientists. The clinical picture is striking, combining spasticity, involuntary movements, and cognitive retardation with self-injurious behavior and the manifestations of gout. Biochemically, the overproduction of uric acid – the end product of purine metabolism – was, when measured, the largest ever seen. The disease is now well understood on a molecular basis. Enzyme analysis and mutational analysis have made available a full range of genetic testing, including diagnosis, carrier detection, and prenatal diagnosis. Therapy with allopurinol has been effective for those manifestations the disease shares with gout. Treatment for the neurological and behavioral features of the disease remains elusive.

Keywords Lesch-Nyhan Disease, uric acid, self-injurious behavior, dystonia, choreoathetosis, hypoxanthine-guanine phosphoribosyltransferase (HPRT)
Review

Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome

Rosa J Torres*1 and Juan G Puig2

Address: 1Division of Clinical Biochemistry, La Paz University Hospital, Madrid, Spain and 2Division of Internal Medicine, La Paz University Hospital, Madrid, Spain

Email: Rosa J Torres* - rtorres.hulp@salud.madrid.org; Juan G Puig - jgarciaPuig@terra.es

* Corresponding author

Published: 8 December 2007


Received: 19 July 2007
Accepted: 8 December 2007

This article is available from: http://www.OJRD.com/content/2/1/48

© 2007 Torres and Puig; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
"A **behavioral phenotype** is a characteristic pattern of behavior consistently associated with a biologic disorder."

Four year old patient was brought to the emergency room because of hematuria (blood in urine).

“An alert intern in the emergency room examined the urine under the microscope and was struck by its enormous content of crystals.”

“They were crystals of uric acid. As well, the concentration of uric acid in the blood was elevated. We knew then that we were dealing with a problem of purine metabolism.”

Deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT) activity is an inborn error of purine metabolism associated with uric acid overproduction.

There is a continuum spectrum of neurological manifestations depending on the degree of the enzymatic deficiency.


A 7-year-old boy with the Lesch-Nyhan disease. Illustrated are the inability to sit without support, choreoathetoid posturing, spasticity, and the left spontaneous Babinski response. The behavior may be visualized in the loss of tissue about the lower lip.

Photo: Reprinted with permission from Nyhan and Ozand, 1998.

- Confused with cerebral palsy.
- Movement disorder (choreoathetosis with dystonia)
  - Delay in motor development
  - Spasticity
  - Deep tendon reflexes
  - Positive Babinski
  - Involuntary movements
  - Cannot walk or sit without assistance
- Some patients have mental retardation however, some are considered to be cognitively normal (parent assessment).
- X chromosome-linked recessive inheritance
  - “It was a disease of the male, but transmission always occurred through the female.”
- Most striking features:
  - Badly mutilated lower lip and fingers
  - Self injury/mutilation
  - If fingers are not bandaged the patient will continue to bite them-compulsive behavior.
  - Normal pain sensation.
  - Injure others – limited b/c of motor dysfunction.
  - Patient will display remorse after hurting self or others.
Care for Lesch-Nyhan syndrome patients is dominated by physical restraints used to protect themselves from self-injury.

Elbow restraints allow hand use without the possibility of finger mutilation.

Patients request the restrictions and become anxious if they are unrestrained.

Dental guards prevent cheek & lip biting

The treatment for Lesch-Nyhan syndrome:

- **Controlling hyperuricemia**
  - nephropathy
  - gout

- **Neurological symptoms**
  - Spasticity, dystonia, and/or dyskinetic movements
  - Hypertonia – treated with diazepam and baclofen

- **Dental extraction and restraints**

Intrathecal baclofen and deep-brain stimulation are also treatment options for L-N syndrome-associated dystonia and spasticity.
Pallidal Deep-Brain Stimulation Associated With Complete Remission of Self-injurious Behaviors in a Patient With Lesch-Nyhan Syndrome: A Case Report

Laura L. Deon, MD¹, Miriam A. Kalichman, MD², Cynthia L. Booth, RN, MS, APN²,³, Konstantin V. Slavin, MD⁴, and Deborah J. Gaebler-Spira, MD¹,⁵

Abstract
The purpose of this case report is to review the management of a boy with Lesch-Nyhan syndrome with deep-brain stimulation who had remission of self-injurious behaviors as a result. This patient was treated with intrathecal baclofen and, later, with deep-brain stimulation to reduce hypertonia. Goals were to improve wheelchair positioning for school attendance and to reduce the use of restraints for comfort. Intrathecal baclofen was implanted twice and decreased the hypertonia, but both were explanted because of infection. Deep-brain stimulation was initiated 2.5 years ago, and since that time, comfort and function have improved and caregiver burden has decreased. Improvements in dystonia with deep-brain stimulation have also occurred, and self-injurious behaviors have resolved.
ITB, intrathecal baclofen; DBS, deep-brain stimulation

Diseases affecting the **pallidum** may result in **movement disorders and obsessive-compulsive disorders**.

Pallidal deep-brain stimulation for the treatment of Lesch-Nyhan syndrome is a relatively new and evolving technique, but results are promising.

Two and a half years after implantation of deep-brain stimulation, our patient continues to have **decreased dystonia and complete absence of self-injurious behaviors**.

To the best of our knowledge, this is the youngest Lesch-Nyhan syndrome patient reported in the literature to undergo the deep-brain stimulation procedure.

Our results support previous reports of successful application of deep-brain stimulation in symptomatic management of Lesch-Nyhan syndrome patients. **Deon, L. L. et. al. (2012) Journal of Child Neurology 27(1) 117-120**
Tourette Syndrome

Neurological disorder

Described in 1885 by Georges Gilles de la Tourette

Patient Madame de D.

Incidence: 1:1000
age onset: 2-25

Madam de D., presently age 26, at the age of 7 was afflicted by convulsive movements of the hands and arms. These abnormal movements occurred above all when the child tried to write, causing her to crudely reproduce the letters she was trying to trace. After each spasm, the movements of the hand became more regular and better controlled until another convulsive movement would again interrupt her work. She was felt to be suffering from overexcitement and mischief, and because the movements became more and more frequent, she was subject to reprimand and punishment. Soon it became clear that these movements were indeed involuntary and convulsive in nature. The movements involved the shoulders, the neck, and the face, and resulted in contortions and extraordinary grimaces. As the disease progressed, and the spasms spread to involve her voice and speech, the young lady made strange screams and said words that made no sense.

Friedhoff & Chase (1982)
Tourette syndrome

- TS can range from mild and non-impairing to severe and incapacitating
- Often, a child with TS has a parent or other close relative with TS.
- Associated with obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD).
- Possible environmental trigger for TS - Strep bacteria have proteins on their surface that resemble proteins in the basal ganglia.

- A neurologic condition called "Sydenham's Chorea" (once referred to as "St. Vitus Dance") occurs after strep throat.
- Like TS, Sydenham's Chorea starts in childhood, has abnormal involuntary movements, can affect mood, personality, or attention, and is believed to come from abnormal function of the basal ganglia.
- Several medical publications have described children with an explosive onset or worsening of tics, obsessions, and compulsions after strep throat.

“urge to action”

- yawning
- Activity in the frontal cortex
- Involuntary movements
- insula
Self injurious behavior

deliberate, non-accidental, repetitive infliction of self harm without suicidal intent

borderline personality disorder, eating disorders, and psychoactive substance abuse

SIB also occurs with some frequency in movement disorders

Self injurious behaviour in Tourette syndrome: correlates with impulsivity and impulse control

C A Mathews, J Waller, D V Glidden, T L Lowe, L D Herrera, C L Budman, G Erenberg, A Naarden, R D Bruun, N B Freimer, V I Reus


Background: Self injurious behaviour (SIB), the deliberate, repetitive infliction of self harm, is present in a wide variety of neuropsychiatric disorders, including Tourette syndrome (TS). Although SIB occurs in up to 60% of individuals with TS, and can cause significant clinical impairment and distress, little is known about its aetiology.

Objective: This study examined the relationship between SIB and other behavioural features that commonly co-occur with TS in nearly 300 subjects with TS participating in three genetic studies. SIB, obsessions, compulsions, tic severity, attention deficit hyperactivity disorder related impulsivity, risk taking behaviours, and rages were systematically assessed in all subjects.

Methods: Using logistic regression, a best fit model was determined for both mild to moderate SIB and severe SIB.

Results: Mild/moderate SIB in TS was correlated with the presence of obsessive and compulsive symptoms such as the presence of aggressive obsessions or violent or aggressive compulsions, and with the presence of obsessive-compulsive disorder and overall number of obsessions. Severe SIB in TS was correlated with variables related to affect or impulse dysregulation; in particular, with the presence of episodic rages and risk taking behaviours. Both mild/moderate and severe SIB were also correlated with tic severity.

Conclusions: This study suggests that mild/moderate and severe SIB in TS may represent different phenomena, which has implications for clinical management of these symptoms.
Self Injurious Behavior in TS

SIB in TS is about 60%:
Examples: compulsive skin picking, self hitting, lip and other self biting, filing of the teeth, head banging, and eye damage from self poking

http://www.youtube.com/watch?v=2kJ1sGShpC0

http://www.youtube.com/watch?v=YOeb-0Oearo
Wariness on Surgery of the Mind

By BENEDICT CARET

In recent years, many psychiatrists have come to believe that the last, best chance for some people with severe and intractable mental problems is psychosurgery, an experimental procedure in which doctors operate directly on the brain.

Hundreds of people have undergone psychosurgery for psychiatric problems, most in experimental trials, with some encouraging results. In 2006, the Food and Drug Administration approved one surgical technique for certain severe cases of obsessive-compulsive disorder or O.C.D. For the first time since frontal lobotomy fell into disrepute in the 1950s, surgery for behavior problems seemed back on the road to the medical mainstream.

But now some of the field's most prominent scientists are saying, 'Not so fast.'

In the current issue of the journal Health Affairs, these experts say approving the surgery for O.C.D. was a mistake — and a potentially costly one. They argue that the surgery has not been sufficiently tested, that neither its long-term effectiveness nor its side effects were well known and that even taking it 'therapy' when people's hopes were beyond what is scientifically supported.

'We're not against the operation, we just want to see it tested adequately before it's called an 'therapy,' said the paper's lead author, Dr. Joseph J. Foss, chief of medical ethics at New York-Presbyterian-Westchester hospital. "With the advent of psychosurgery, it's important that we don't misinterpret things as therapy when they're not."

Doctors who run programs offering the operation strongly object. "These patients are very capable of making informed decisions based on our experience with the surgery," said Dr. Wayne K. Goodman, chairman of psychiatry at the Mount Sinai School of Medicine, "and I would not want to deprive them of the option."

More than I would deny someone with access to an experimental therapy that has not been established yet. Their lives have been so destroyed by O.C.D. that they might contemplate suicide if the surgery were not available.

The debate on this question — should experimental surgery be allowed, in some cases, before long, costly trials are completed — will greatly set the future course of modern psychosurgery. And it may turn on the interpretation of an arcane Food and Drug Administration regulation that allows manufacturers to put a device on the market without rigorously proving its effectiveness when it is intended to treat or diagnose a fairly rare condition.

It was this exemption that the agency applied in 2006 to a device used to perform so-called deep brain stimulation, or D.B.S., for patients with obsessive-compulsive disorder who had not been helped...
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babinski</td>
<td>A reflex movement in which when the sole is tickled the great toe turns upward instead of downward and which is normal in infancy but indicates damage to the central nervous system (as in the pyramidal tracts) when occurring later in life.</td>
</tr>
<tr>
<td>Deep tendon reflexes</td>
<td>In a normal person, when a muscle tendon is tapped briskly, the muscle immediately contracts due to a two-neuron reflex arc involving the spinal or brainstem segment that innervates the muscle. The afferent neuron whose cell body lies in a dorsal root ganglion innervates the muscle or Golgi tendon organ associated with the muscles; the efferent neuron is an alpha motoneuron in the anterior horn of the cord. The cerebral cortex and a number of brainstem nuclei exert influence over the sensory input of the muscle spindles by means of the gamma motoneurons that are located in the anterior horn; these neurons supply a set of muscle fibers that control the length of the muscle spindle itself.</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>Is an absent or diminished response to tapping. It usually indicates a disease that involves one or more of the components of the two-neuron reflex arc itself.</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Refers to hyperactive or repeating (clonic) reflexes. These usually indicate an interruption of corticospinal and other descending pathways that influence the reflex arc due to a suprasegmental lesion, that is, a lesion above the level of the spinal reflex pathways.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Dystonia is a movement disorder which causes involuntary contractions of your muscles. These contractions result in twisting and repetitive movements. Sometimes they are painful. Dystonia can affect just one muscle, a group of muscles or all of your muscles. Symptoms can include tremors, voice problems or a dragging foot. Symptoms often start in childhood. They can also start in the late teens or early adulthood. Some cases worsen over time. Others are mild. Some people inherit dystonia. Others have it because of another disease. Either way, researchers think that a problem in the part of the brain that handles messages about muscle contractions might cause dystonia. There is no cure. Instead, doctors use medicines, surgery, physical therapy and other treatments to reduce or eliminate muscle spasms and pain.</td>
</tr>
</tbody>
</table>