Lesch-Nyhan Syndrome

Alternative names: Historically, Lesch-Nyhan syndrome is the designated term for this disease. Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT, HGprt) deficiency are also used to describe this disease. In addition to the classic form of LND, Jinnah and others have characterized two variant forms of the disorder -- these individuals have higher levels of enzyme activity than patients with the classic form and do not have the feature of self-injurious behavior. Elevated levels of uric acid is present is all three types of LND.

First description: It is interesting that the first description of Lesch-Nyhan Disease may have been in the year 1267. Beck (Euro J of Ped Surg 1991) identified an original description of what may be LND when he uncovered cases of self-injury, gout, and mental retardation in individuals living in a small village in England where St. Thomas, Archbishop of Canterbury, had been killed. The original account, written by Jacobus de Voragine, suggested the disease might somehow be related to the murder of St. Thomas and the "wrath of God". We have come slightly further in our understanding of the disorder since then … and since the first description of the familial nature of the disease by Dr. Nyhan, and his medical student, who published data in 1964 on two brothers with LND in the American Journal of Medicine 36, 561 –570. Nyhan followed up this first article with a second article in 1965, A familial disorder of uric acid metabolism and central nervous system function in J of Pediatrics, 257 – 263. Not only was Nyhan the first to describe the familial nature of the disease, he has devoted his career to the study and care of patients with a variety of metabolic disorders including LND.

In 1959, two physicians, Catel and Schmidt, described what has turned out to be the first variant of the disorder of partial HPRT deficiency (Kelley-Seegmiller syndrome) which, in turn, involves a variable degree of neurological symptoms without the self-injurious behavior of LND. Two variants of classic LND have been further characterized by Dr. Jinnah and colleagues. Seegmiller discovered the enzyme defect in the purine salvage pathway in 1967. Of interest, in 1960, Riley described gout and cerebral palsy in a 3 year old that may be the first classic case of LND in the literature. Hoefnagel et al, in 1965, were the first to suggest it was X-linked. In 1983, Wilson and Kelly identified the first specific mutation at the molecular level: a single nucleotide change in the codon for aspartic acid 193 -- GAC for AAC. This discovery has turned out to be one of many, many different nucleotide changes identified in this gene!

Due to the nature and importance of the purine salvage pathway, it is entirely likely that numerous cell processes and cell lines function abnormally. Although this area of research is in its infancy, Dauphinot et al, using microarray analysis, recently suggested biological processes involving cell-division processes and metabolic and nucleic acid processes, are dysfunctional.

Incidence: This is a rare disorder that has an accepted incidence of about 1:380,000.

Genetic aspects: Lesch-Nyhan Disease (LND) is a rare X-linked, recessive genetic disorder of the purine salvage pathway and is associated with cognitive impairment, hyperuricemia, renal involvement as well as the hallmark symptom of severe and involuntary self-injurious behaviors. The movement disorder is best characterized as dystonia superimposed on hypotonia. Although LND is appropriately considered a metabolic disease involving the absence, or near absence of the enzyme HPRT, it is best thought of as a disorder of the basal ganglia. Understanding the neurological manifestations of this enzyme defect allows for a thorough understanding of the disorder and subsequent comprehensive management strategies.

There are probably a few thousand individuals with this disease in the world. The mutations are in the HPRT1 gene located on the long arm of the X chromosome. Remarkably, over 600 different mutations have been identified in different families (O'Neill and others). The product of the normal gene is the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) which recycles purines from DNA and RNA. Because it is an X-linked recessive mutation, it ought to occur only in males, but there have been several documented cases in females – thought to be a consequence of events explained by the Lyon Hypothesis. Since the 1960's we have known that because of the lack of HPRT, there is an over-production of uric acid and subsequent uric acid stone formation. (Xanthine stone formation is due to dose specific issues of allopurinol.) Unfortunately, treatment of the elevated serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease.

Physical phenotype and the basal ganglia: Among other deficits, patients with LND have reductions of dopamine in the basal ganglia and it is tempting to think of this disease as a basal ganglia disorder, even though other areas of the brain are involved as well. From the motor disorder standpoint, LND is best described as dystonia superimposed upon hypotonia, although chorea, spasticity and athetosis have been described. During volitional movements, the examiner may believe increased tone is present, yet when the movement is over or when the patient is relaxed, hypotonia is clearly evident. Further, anxiety often confuses the clinical picture, as it does with other aspects of the disorder, especially when the patient is examined by a physician unfamiliar with the patient. The question of the presence of athetosis vs dystonia and the presence of hypotonia vs spasticity is often difficult to distinguish on exam by a physician who is not familiar with the behavioral manifestations of LND. LND presents in the first few months of life as a developmental delay and may be diagnosed initially as cerebral palsy. Individuals with classic LND are generally non-ambulatory. The basal ganglia is known to be involved in the regulation of areas other than the motor circuits, including personality, cognition and emotion. Visser, Bar, and Jinnah have reviewed in depth the involvement of the basal ganglia in LND, and their paper started a frame-shift in our understanding of the neurological aspects of the disease.

Cognitive aspects: Although there may be significant bias and scatter, depending on who administers the IQ testing, the range of IQ scores varies but is generally in the mild to moderate mentally retarded range although some authors feel that it is lower, ranging from 40 to 80. The LND behaviors and neurological problems limit the validity of standard IQ tests. Patients with LND can by very engaging and personable and are often able to recount scores of local sporting events on a routine basis. It is interesting that parents often believe IQ scores obtained are artificially low and reason that low performance is secondary to LND behavior.

Is there evidence to suggest that there is a greater degree of dysfunction of neurons in the basal ganglia than the cortex or the fibers that descend from the cortex? This is an interesting question that requires further study (Gottle et al).

Behavioral aspects: The behavioral phenotype of Lesch-Nyhan Disease, physical and emotional self-injury, including severe self-mutilation and aggressive behavior, are generally involuntary in nature. The self-injurious behavior is not under the patient's control nor does the patient desire it. These self-destructive behaviors usually begin between ages three and six and often escalate as the patient ages and the patient is more physically able to cause self-injury. The first manifestations of physical self-injury are lip biting, finger biting, and biting of the oral cavity. Modes and patterns of self-injury have been previously described in Robey et al, and are often specific to each individual patient and appear consistent over the life-span. Patterns of association involve self injury to or about: 1) external surfaces or 2) oral or biting, usually of the lips and fingers. If a patient tends to injury him or herself using external surfaces, this pattern tends to continue throughout the life-span. If the self-injury involves oral cavity or biting, then this pattern will reoccur throughout the life-span. Forms of

self-injury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in doorways. Emotional self injury, or outwardly directed aggressive behaviors, include hitting, kicking, head-butting, biting others, spitting, swearing, ethnic slurs, inappropriate remarks to the opposite sex, frequently changing opinions, and/or lying.

When oral self- injury is present, removal of the teeth is essential to prevent facial disfigurement. Removal of teeth is often difficult for families (and healthcare providers) to accept, however the teeth, when not removed, can be destructive. Decisions regarding dental extraction must be made with physicians who are expert in the comprehensive care of patients with this disorder (www.Lesch-Nyhan.org; Goodman, et al.)

Treatment: Allopurinol is used to lower the elevated serum uric acid. Historically, levels of the serum uric acid have been kept in a range that minimizes the formation of uric acid stones, yet not too low as to lead to the formation of xanthine stones. Nyhan (personal communication) has suggested that further work needs to be performed to address this clinical issue. Certainly, by lowering serum uric acid with allopurinol, death due to chronic renal failure has become quite rare.

Treatment for the behavioral manifestations of LND is multi-modal and should include: 1) judicious use of protective devices, 2) utilization of a behavioral technique commonly referred to as selective ignoring with redirection of activities, and 3) occasional use of medications.

The use of medications for treating the behavioral component of this disorder is controversial yet most children and adults with LND are treated with different medications. No medication has been found to reverse the so-called 'Lesch-Nyhan behaviors', either motor or behavioral. Selective ignoring is a methodology that is designed to extinguish self-destructive emotional or physical behavior in the LND patient. It requires the caretaker to ignore such behavior by the LND patient towards said caretaker so that the behavior decreases or ceases. Along with selective ignoring, the use of redirection is also found to be helpful. At times controversial, the use of protective devices is essential, yet often problematic for patients and institutions not familiar with the care of LND patients. Professionals unfamiliar with LND may perceive the use of these protective devices from a traditional paradigm of restraints – which is to say, the use of these devices against a patient's will. When protective devices are requested by the patient -- and used to safeguard the patient from him or herself -- the outcome is an extraordinary feeling of comfort and safety. Not allowing the use of protective devices when requested violates the autonomous rights of the patient. In Lesch-Nyhan Disease self-injury far exceeds that associated with other developmental disabilities, and, of course, is a consequence of the neurotransmitter and cell function abnormalities characterizing the disorder. Although not all individuals with this condition demonstrate severe behavioral manifestations, it is reasonable to say that all benefit from the use of protective devices at some point during their lifetime. It is extremely important to note that the Joint Commission and the US government's CMS requirements both include exceptions to the restraint standards for patients with LND. Issues regarding removal of teeth is addressed above (See exceptions to the CMS standard: 482.13. (e) (6).)

Deep Brain Stimulation (DBS) has been tried in numerous patients worldwide with LND to decrease the degree of dystonia. In this procedure neurosurgeons place two stimulators in the basal ganglia, similar to the stimulators used in other movement disorders such as Parkinson's disease. The results suggest a decrease in dystonic movements as well as a decrease in self-injurious behavior; however it is unclear if this will become a standard treatment option due to variable effects and complications of the surgery.

Life expectancy: Life expectancy is a difficult issue to address as the extent of the associated clinical conditions of Lesch-Nyhan Disease has not yet been fully characterized. Fortunately, due to the use of allopurinol, which acts as a substrate for xanthine oxidase, patients with this disorder should no longer die of renal complications. There is a suggestion that some patients may die suddenly in their

twenties and thirties possibly as a consequence of an unexplained neurological event. Certainly, as the accompanying clinical conditions are managed a longer life expectancy can be anticipated.

Key references:

www.Lesch-Nyhan.org

Jinnah H., Friedman, T. Lesch-Nyhan Disease, Chapter 107, In the Metabolic and Molecular Basis of Inherited Disease, 8th Edition, Scriver, CR, Beaudet, AL, Sly, WS, Valle, D., Eds. (2001).

Catel, W, Schmidt, J, On familial gouty diathesis associated with cerebral and renal symptoms in a small child. Dtsch Med Wochenschr. 1959 Nov 27;84:2145-7.

Wilson, JM and Kelley, WN, Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in a patient with the Lesch-Nyhan syndrome,

J Clin Invest. 1983 May; 71(5): 1331–1335.

Riley, ID. Gout and Cerebral Palsy in a three year old boy. Archives of Disease in Childhood, 1960, 293-294.

Visser, JE, Bar, PR, and Jinnah, HA. Lesch-Nyhan Disease and the basal ganglia. Brain Research Review 32 (2000) 449-475

Hoefnagel, D, Andrew, E. D., Mireault, N. G., Berndt, WO, Hereditary choreoathetosis, self-mutilation and hyperuricemia in young males. New Eng. J. Med. 273: 130-135, 1965.

Nyhan W. Clinical features of the Lesch-Nyhan syndrome, Arch Int Med 130 (1972) 186-192.

Harris, J. Lee, Jinnah, H et al. Craniocerebral Magnetic Resonance imaging measurement and findings in Lesch-Nyhan Syndrome. Arch Neurol, (1998) April vol 55, 547 – 553.

Jinnah HA, De Gregorio LJ, Harris JC, Nyhan WL, O'Neill JP. The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. Mutat Res 463: 309 – 326, 2000

Robey, K, Reck, J, Giacomini, K, Barabas, G and Eddey, G: Modes of self – mutilation and their patterns of association in persons with Lesch – Nyhan disease, Dev Med Child Neur (2003) 45, 167 – 171.

Puig JG, Torres RJ, Mateos FA, Ramos TH, Arcas JM, Buno AS, O'Neill P. The spectrum of hypoxathine-guanine phosphoribosyltransferase (HPRT) deficiency: clinical experience based on 22 patients from 18 spanish families. Medicine (Baltimore); 80: 102 – 112, 2001.

Visser J., Harris J., Barabas G, Eddey G., and Jinnah, H. The Motor Disorder of Classic Lesch–Nyhan Disease. Nucleosides, Nucleotides & Nucleic Acids. Vol 23, pp 1161 – 1164, 2004.

O'Neill, P. Mutation Carrier Testing in Lesch-Nyhan Syndrome Families: HPRT Mutant Frequency and Mutation Analysis with Peripheral Blood T Lymphocytes. Genetic Testing. April 2004, Vol. 8, No. 1, Pages 51-64.

CMS standard: 482.13. (e) (6).) Exception: "Repetitive self-mutilating behavior. If a patient is diagnosed with a chronic medical or psychiatric condition, such as Lesch-Nyhan Syndrome, and the patient engages in repetitive self-mutilating behavior, a standing or PRN order for restraint to be applied in accordance with specific parameters established in the treatment plan would be permitted.

Since the use of restraints to prevent self-injury is needed for these types of rare, severe, medical and psychiatric conditions, the specific requirements (1-hour face-to-face evaluation, time-limited orders, and evaluation every 24 hours before renewal of the order) for the management of violent or self-destructive behavior do not apply."

Disappearance of self-mutilating behavior in a patient with Lesch–Nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. T Akaomi, et al. J Neurosurg 98:414–416, 2003.

Purine metabolism during neuronal differentiation: the relevance of purine synthesis and recycling. Göttle M, Burhenne H, Sutcliffe D, Jinnah HA. J Neurochem. 2013 Dec;127(6):805-18. doi: 10.1111/jnc.12366. Epub 2013 Aug 18.

Nucleosides Nucleotides Nucleic Acids. 2014;33(4-6):208-17. doi: 10.1080/15257770.2014.880477. Transcriptomic approach to Lesch-Nyhan disease. Dauphinot L1, Mockel L, Cahu J, Jinnah HA, Ledroit M, Potier MC, Ceballos-Picot I.

Consequences of Delayed Dental Extraction in Lesch-Nyhan Disease. Goodman,

Torres, Puig and Jinnah. Movement Disorder; Published online: 6 JUN 2014.

Gary E. Eddey, August 2014
