SSBP Syndrome Sheets

Lesch-Nyhan Disease (LND)

First Description & History

Historically, Lesch-Nyhan syndrome is the designated term for this disease; however, Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT, HGprt) deficiency are also used to describe this disease.

It is interesting that the first description of Lesch-Nyhan Disease may have been in the year 1267. Beck in 1991, identified an original description of what may be LND when he uncovered several cases of self-injury, gout, and intellectual disabilities 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 that 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 (Nyhan et al. 1964, 1965).

Nyhan was the first to describe the familial nature of the disease. His work demonstrated that mutations in the hypoxanthine guanine phosphoribosyl transferase (HPRT) gene, leads to the lack of its enzymatic activity. Dysfunction of HPRT, disrupts the purine metabolism, adversely influencing neurodevelopment and leading to the neurobehavioral phenotypes (Nyhan, 1997) and to an excess of uric acid with many systemic consequences including hyperuricemia, formation of bladder calculi, and painful gouty arthritis. (Torres et al.2007). However, HPRT deficiency results in a broad spectrum of clinical involvement, which depends on the severity of the enzyme deficiency, where an activity of less than 1.5%, is at the severe end of the spectrum. Two less severe variants include HPRT related hyperuricemia, known as Keeley–Seegmiller syndrome which present with an enzymatic activity varying from 8% to 60%, and hyperuricemia with neurological disability, characterized by an enzymatic activity of 1.5-2% with hyperuricemia and neurological symptoms (Nanagiri and Shabbiri 2022).Measurements of blood HPRT activity is still, to date, the gold standard for diagnosing LNS (Nyhan, 2005).

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 (2010). 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 are commonly present in all three types of LND. 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-years 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!

Incidence and Epidemiology

LND is a rare inborn error of metabolism disorder that affects mainly males with an estimated incidence between 1:235,000 and 1:380,000 live births in the US (Torres et al. 2007). Studies show that it occurs in relatively equal frequencies in all populations. Because it is an X-linked recessive mutation, it ought to occur only in males, but there have been several documented cases in females – although the lower severity and penetrance can be likely explained by the Lyon hypothesis, so that males who receive from the carrier mothers, the X chromosome carrying the mutated gene, will express the disease while

females are mostly carriers but can develop the disease if X chromosome carrying the defective gene is expressed phenotypically.

Genetic aspects

LND is a rare X-linked, recessive genetic disorder caused by a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme, located at a q26-27 position on the long arm of the X chromosome (Figure 1).

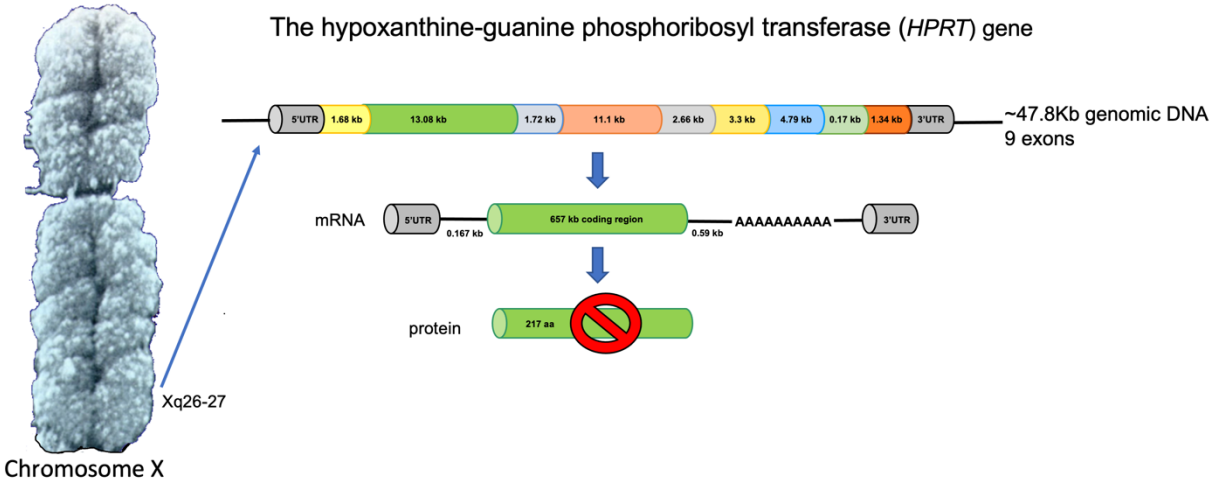

Figure 1. The HPRT gene is located on chromosome X q26-27. It spans approximately 48Kb of genomic DNA and contains 9 exons. The gene encodes for a 217 amino acid protein, which lack of function leads to functional significant purine overproduction and ultimately to neural problems.

The enzyme is a transferase that catalyzes the conversion of hypoxanthine into inosine monophosphate and of guanine to guanosine monophosphate. This enzyme plays a central role in the generation of purine nucleotides through the purine salvage pathway (Figure 2).

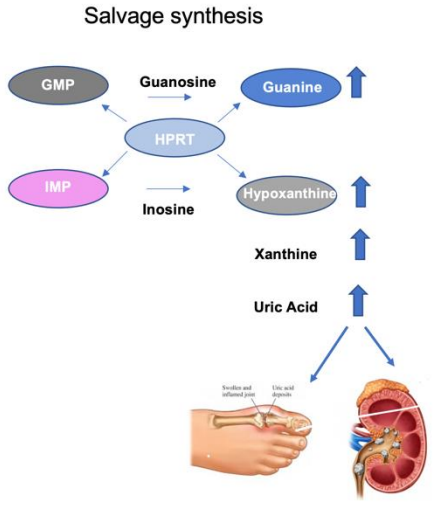

Figure 2. Deficiency of salvage nucleotide synthesis. LND is caused by the deficiency of the purine salvage enzyme HPRT which is responsible for the conversion of hypoxanthine into inosine monophosphate (IMP) and of guanosine into guanosine monophosphate (GMP). After their synthesis they are converted to nucleotides that are used for DNA repair and synthesis. The lack of HPRT also leads to increased uric acid, which accumulation leads to gout and kidney stones.

Lack of the enzyme causes an increase in guanine and hypoxanthine, which eventually gets converted into uric acid. There are probably a few thousand individuals with this disease in the world. The

mutations are within 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 et al. 2004), each leading to varying levels of severity of clinical presentations making HPRT enzyme deficiency a spectrum rather than a single disease (Fu et al. 2014).

Clinical, cognitive, and behavioral features

Individuals with LND are asymptomatic at birth with normal prenatal growth and development. Typically hyperuricemia is present at birth, and orange-colored crystals in the diapers is the only clinical evidence hyperuricemiam, which leads to crystalluria, urolithiasis, nephrolithiasis, gout, and juvenile arthritis. In addition to hyperuricemia, LND is associated with cognitive impairment, renal involvement as well as severe and involuntary self-injurious behaviors.

Although it is appropriately considered a metabolic disease involving the absence, or near absence of the enzyme HPRT, because among other deficits, patients with LND have reductions of dopamine in the basal ganglia, 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 clear. 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 are known to be involved in the regulation of areas other than the motor circuits, including personality, cognition, and emotion (Visser et al. 2000).

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 intellectual disability 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 be 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.

The behavioral phenotype of LND, physical and emotional self-injury, including severe self-mutilation and aggressive behavior, are generally involuntary in nature, thus, not under the patient's control. These self-destructive behaviors, one of the hallmarks of LND, 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 lifespan. 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 lifespan. If the self-injury involves oral cavity or biting, then this pattern will re-occur throughout the lifespan. 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. 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).

Treatment

Management of LND syndrome is complex, thus understanding the neurological manifestations of HPRT defect allows for a thorough understanding of the disorder and subsequent comprehensive management strategies.

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, the xanthine urolithiasis (xanthine stone formation is due to dose specific issues of allopurinol.) Allopurinol is a drug that blocks the conversion of hypoxanthine and xanthine to uric acid by inhibiting the xanthine oxidase enzyme, representing the cornerstone of treatment of hyperuricemia. Although Allopurinol is used to lower the elevated serum uric acid, it must be titrated to maintain serum uric acid in the critical window that attenuates the neurologic and systemic consequences of hyperuricemia while avoiding xanthine stone formation. 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. Unfortunately, treatment of the elevated serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease. However, as previously mentioned, since the hyperuricemia is present early during the development, early intervention can avoid many potential complications.

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 LND 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.

Deep Brain Stimulation (DBS) has been tried worldwide in numerous patients with LND to decrease the degree of dystonia. In this procedure neurosurgeons place two stimulators in the basal ganglia, like 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. Finally, the use of gabapentin and botulinum injections have been tried with somewhat a reduced self-abusive behavior (Dabrowski et al. 2005).

Life expectancy

Life expectancy is a difficult issue to address as the extent of the associated clinical conditions of LND 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 because of an unexplained neurological event. Certainly, as the accompanying clinical conditions are managed a longer life expectancy can be anticipated.

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