An Overview of Lesch-Nyhan Syndrome

Abstract

Lesch-Nyhan Syndrome is a disorder that strikes the sufferer with debilitating motor and cognitive problems, hyperuricemia, and the urge to do harm to yourself with acts of self-injurious behavior. Research has lead to the discovery of a genetic sequence that results in a defective enzyme, but researchers are still unsure how this leads to the neurological and behavioral problems that are the hallmark of the disorder. Treatments as simple as wearing oven mitts and as complicated as electrical wiring in the brain have been used to help LNS patients, but no cure for the syndrome seems in sight.
**Introduction**

In the world of developmental and physical disorders none is stranger than Lesch-Nyhan Syndrome. It brings with it a variety of physical ailments but the defining feature of the condition is behavioral. The sufferer seems to be overtaken with an involuntary uncontrollable compulsion to destroy themselves and those around them.

In the autumn of 1962, a young mother brought her four year old son to the pediatric emergency room at Johns Hopkins medical center. The boy had previously been diagnosed with cerebral palsy and could not walk or sit up. He was experiencing pain when he urinated. His mother told the resident who was examining the boy that he had “sand in his diaper” (Preston, 2007). The young boy was admitted to the hospital. The resident and an intern began examining the “sand” from the boy's diaper. It was full of crystals and eventually it was determined that they were the result of an overproduction of uric acid, a waste product usually excreted by the kidneys. Uric acid is what causes gout and usually appears in older men, why would this boy have so much in his system? Wanting to get a second opinion the resident consulted Dr. William L. Nyhan, a research scientist who had a lab on the premises. Dr. Nyhan summoned his medical student, Micheal Lesch. Together they went to examine the boy.

They found that the boy, Matthew, was much more than a simple case of a child with cerebral palsy. They found profound retardation of motor development and repetitive involuntary slow writhing movements, a disorder known as choreoathetosis (Nyhan, 2005). He seemed alert and tried to communicate with the doctors but had trouble due to the presence of dysarthria, an inability to control the muscles that make speech (Preston, 2007). They looked for signs of gout and found none. Then they noticed that Matthew's hands were bound and covered in gauze. They asked for him to have his bandages removed and the young patient went wide
eyed as if scared. When his hands were exposed they saw that the tips of Matthew's fingers were missing. It was at this time that the doctors noticed that Matthew had bite damage around his lips as well. Matthew then began to cry and thrust his hands towards his mouth. The doctors were horrified as they realized that Matthew had chewed off his own fingers and parts of his lips and needed to be stopped from doing any more damage at that very moment. They helped Matthew get back into his restraints. What would make this little boy want to chew off his face and hands? While discussing what they had seen they found out that Matthew had a brother, Harold, who was showing the same symptoms. They asked Matthew's mother to examine Harold as well.

Two years later the doctors published the first paper on the disease that now bears their names, Lesch-Nyhan Syndrome (LNS). Their paper stated the basics of the disorder as follows, “A syndrome consisting of hyperuricemia, mental retardation, choreoathetosis and self-destructive biting has been described in two brothers aged five and eight years old” (Lesch & Nyhan, 1964). It was very interesting to the medical community for a number of reasons. First, it seemed to be a genetic disorder. With brothers in families having the disorder with healthy sisters and mothers, it was likely X-based, dealing with the twenty-third chromosome pair, the pair that determines sex. Secondly, it was a metabolic disorder with exceptional results, as the uric acid present was at levels that had never been seen before. Third, it was a metabolic disorder that had a behavioral phenotype, a characteristic pattern of behavior associated with a biological disorder (Nyhan, 2005), and it was a pattern of abnormal behavior that was considerably memorable, the self injurious behavior of trying to bite off one's fingers and lips as well as other acts of self harm.

Shortly after they published their findings more cases of LNS began to be recognized.
They were always in males, only recently has a female patient has been discovered (Nyhan, 2005). One family alone had fifteen separate cases. Why were these children so sick? Was it the body's reaction to the Uric acid? Was it genetic? What was the reason for the self harm? Was there really a genetic basis for behavior?

Our look at LNS begins by looking at some of the unique characteristics of this illness and learning about some of the people who suffer from this disease. Then we will take a look at the etiology of the disorder and begin to discover the why and the how of this destructive condition. Lastly, we will take a look at some prevention and treatment methods available to the people who suffer with it. We will travel from metabolism disorders to genetics to the strange world of self-injurious behavior. We will learn about a scientist who had to learn about LNS rather quickly when an experimental rat under his care began to chew his paws off. We will learn about treatments as simple as mouth guards and as complex as deep brain stimulation. After we are done you will never bite your fingernails in quite the same way ever again.

**Characteristics**

There is no average case of LNS. Only an estimated 1 in 380,000 live births are affected (Nyhan, 2005). Patients vary in many ways but all seem to have impairments to some degree in all of three different areas. One, they are hyperuricemic, the condition of having an over abundance of uric acid in their bodies. Two, they suffer from some degree of neurological damage. Almost all are wheelchair bound with the majority of cases suffering from motor development retardation. They appear normal when they are born but by about the third month they are unable to lift their heads or sit up. They display hypotonia, a lack of muscle tone, and many also suffer from dystonia, a lack of motor control, as well. There is often a diagnosis of
mental retardation. Many people now believe that the cognitive impairment is less than once thought and there are some people with LNS who are considered normal in this respect, but LNS patients are nearly impossible to test. As Dr. Nyhan has said in response to this situation, “[h]ow do you measure someone's intelligence if, when you put a book in front of them, he has an irresistible urge to tear out the pages?”

Lastly, all people with LNS display some degree of abnormal behavior, specifically, the self-injuring of one's self by biting. This behavior begins as soon as the child's teeth come in and typically results in parents frantically calling pediatricians asking why their children are trying to eat themselves. LNS sufferers report that they feel as if someone else is controlling them as they bite at their lips and hands until they are bloodied. The self injurious behavior does not stop at biting though. LNS sufferers have been known to stab themselves in their eyes with sharp objects and some have bitten off their tongues (Preston, 2007). Their self-injurious behavior has been described as clever and and not limited to the standard self injurious behaviors of self hitting and head banging. The self-injurious behavior is said to be complex, often involving devious plots (Luiselli, Matson & Singh, 1992) to become unrestrained and hurt themselves.

Their injurious behavior does not stop with themselves. LNS sufferers have been known to punch their doctors, (Nyhan, 2005) punch their friends, and even roll their wheelchairs out into the middle of traffic as they yell at the cars not to hit them because it's the LNS that's making them do it (Preston, 2007).

What adds to the mystery of all this behavior is the fact that many LNS sufferers are described as extremely kind natured. People with LNS will begin to apologize the minute they do something inappropriate to themselves or others. Matthew, the boy under Dr. Nyhan's care in 1962, would often rip the doctor's glasses from his face and hurl them across the room. Before
the glasses would hit the ground Matthew would begin apologizing yelling “Sorry, I'm sorry.” A person with LNS will often apologize for acts he has not committed yet. Dr. Nyhan believes this aspect of their personality has something to do with the disorder as he knows the majority of LNS sufferers in the US (there are only a few hundred) and describes them as “great people” (Preston, 2007). A small review of pictures of children with LNS will almost always show them in seemingly good spirits as they smile through their damaged lips (Maramattom B.V., 2005). Even in the face of this strange unfortunate condition they seem happy. It's another aspect of this disorder that makes it difficult to understand.

LNS sufferers do not have an absence of pain as many believe they must in order to hurt themselves the way they do. They feel everything they do to themselves, often crying and screaming during the acts. They need to be restrained to keep from injuring themselves. They often eat with wide plastic spoons to keep from stabbing themselves. LNS caregivers tasked with restraining people will tell you that in all situations being restrained makes the LNS sufferer happy. They are assured when they know they can't hurt themselves or others and a feeling of calm comes over them.

The prognosis for LNS is very poor. Many patients die in their teens and early twenties and are often very fragile. One such patient inadvertently threw his neck back so hard he broke his neck. LNS sufferers die from kidney failure in most cases and are also susceptible to infections. Many die suddenly and with no explanation, though recent studies show it may have something to do with a failure in respiration processes (Neychev, 2006). Some live into their thirties and beyond. One of the oldest known men with LNS is a gentleman named James Elrod. He was the source for all of the LNS background information used in Richard Preston's book “The Cobra Event”, a novel about a super virus that mimics the effects of LNS. He is now forty-
nine years old.

**Etiology**

What causes this disorder? In 1967, J. Edwin Seegmiller, a research scientist at the National Institute of Health, made a breakthrough discovery. In LNS patients a protein called hypoxanthine-guanine phosphoribosyl transferase (HPRT) does not seem to work correctly. This enzyme is present in all cells in the human body and is tasked with helping to breakdown compounds called purines. Healthy cells are always breaking down and recycling DNA. The DNA is broken down to its four basic building blocks and two of them, adenine and guanine, are purines. If HPRT is not functioning properly these purines, guanine in this case, do not get recycled and reused, creating a metabolism problem: eventually these unused purines build up in the cells. They are soon broken down into the waste product uric acid within the cell. This then permeates the blood and eventually shows itself as crystals in the urine. While in some cases of gout or renal stone disease it has been shown that there is abnormal functioning of HPRT, in the LNS sufferer the HPRT activity approximates zero (Nyhan, 2005). This has become the gold standard of diagnosis for LNS, completely non functioning (1.5% or less) HPRT. We now know why the uric acid is so high in the person with LNS, the enzyme HPRT is defective, but why?

In the days after Lesch and Nyhan discovered Matthew and Harold at Johns Hopkins in the autumn of 1962, LNS was thought to be a genetic in origin. When a disorder appears in two brothers while the father, mother, and sisters remain healthy it suggests that it is X-linked recessive. Since almost all cases of LNS are found in males the search for a genetic cause to the defective HPRT began at the twenty-third chromosome.

In X-linked recessive disorders there is a malfunction of the X chromosome given to a
male by his mother. We all have twenty-three chromosome pairs in our cells. The twenty third pair is the one that determines our sex. Women have two X chromosomes and males have an X and a Y. If a mother is a carrier of a genetic disorder it means one of her two Xs is defective. The condition does not manifest itself in the mother's phenotype, her outward genetic expression, because she has another healthy X chromosome that can repress the mutation in her defective X. But, if she passes on the defective X to a son, he does not have another healthy X to repress the effects of the disorder, the father has given the son a Y. In this case the condition will manifest itself. This process also means that there is a fifty-fifty chance that a carrier's daughter is also a carrier, as she can get the defective X from her mother but never show it because the healthy X she received from her father will repress the effects. The only way a woman can get an X-linked recessive disorder is in the rare case where a father's X is newly mutated for the disorder or the father is a sufferer of the very same disorder the mother carries. In cases of LNS males rarely reproduce, so passing a damaged X to a daughter rarely happens. Common examples of X-linked recessive disorders are hemophilia and red-green color blindness. Less common are Hunter's syndrome and LNS.

In the eighties, researchers decoded the sequence in the human genome that contains the instructions, the letter combinations, for making HPRT. There are six hundred and fifty-seven letters that make up this gene, a segment of genetic information that taken as a whole defines or marks a trait. As expected its locus, its location, was on the X chromosome. Armed with this information researchers began to sequence this gene in people who had LNS. In every case there was a mutation found in the HPRT gene. Not all of the mutations were the same, there were different codings for different families, and in the majority of cases there was only one misspelling in the code. In Preston's (2007) article for the New Yorker, “An error in the code”,
he describes the nature of the situation as follows, “an American boy known as D.G. Had a single G replaced by an A, one out of the three billion letters of code in the human genome. As a result, he was tearing himself apart.”

So, we now know that the person with LNS received a X which coded for non-functional HPRT from his mother. Without working HPRT the cells of the body cannot metabolize purines properly resulting in an overproduction of Uric acid. That explains the hypouricemia, but what about the neurological and behavioral aspects of LNS? What's causing them? This area remains unexplained, but there are some popular theories.

Most discount that it could be the effects of the uric acid itself. There have been cases where children have been treated for elevation of uric acid from birth and even though their bodies never experience a high level of uric acid, they still manifest the neurological and behavioral symptoms of LNS (Luiselli, et al., 1992). Uric acid toxicity as a cause of the developmental disorders seems to be taken off the table by this finding. Many have posited that uric acid, an irritant, may be leading LNS infants to chew at their lips, but this connection has never been shown either (Luiselli, et al., 1992).

It may have to do with a lack of usable purines during development. If a system does not have the HPRT enzyme to reuse DNA components perhaps this leads to problems? It seems logical that a defective enzyme used to recycle DNA would have an adverse effect on early development when neuronal growth is taking place, but where should we look for these effects? If something is going to affect motor development we would look for changes in the Basal ganglia, an area of the brain associated with cognition and motor function. In the early part of the twentieth century people with lesions in this area often showed symptoms of Parkinson's disease. People who study LNS, the seeming opposite of Parkinson's, whose main symptom is
the inability to start an action while LNS displays the inability to inhibit, are of the opinion that answers to some of their questions lie here as well (Luiselli et al., 1992). The neurotransmitter dopamine must be properly transmitted within the Basal ganglia or serious motor or cognitive deficits can occur. It leads to the question of whether dopamine production and use is normal in people with LNS. This brings us to the tale of the neonate-lesioned rat.

In 1973, to examine the effects of reduced dopamine in the brains of rats, George Breese, a researcher at the UNC school of medicine, was lesioning (lesion meaning a loss of function and not an wound or injury) adults rats so they would not produce normal amounts of dopamine. This yielded promising results, but he also wanted to see the effects of a lack of dopamine on a young developing rat. Towards this goal they developed a technique to lesion a neonatal rat. Breese and his colleagues were amazed as the baby rats they had lesioned began to chew off their paws and genitals (Breese et al., 2005). It seemed that by lesioning the rats during their development they had inadvertently created rats with LNS. These findings seem to point towards a lack of dopamine in the developing system as a possible cause of the self-injurious behavior in LNS. Recent research backs up these claims (Neychev VK. Mitev VI., 2004). While a compound to stop this behavior has been found for the rats, there is still no such compound for use with humans.

Another theory points towards a model of a malfunctioning dopamine system where accidental injury is rewarded and reinforced, causing the LNS patient to continue hurting themselves (Zilli EA., Hasselmo ME., 2008). There have been around twenty autopsies on patients with LNS over the years. While their brains look normal, there is as much as eighty percent less dopamine in the Basal ganglia when compared to the average person (Preston, 2007). Similar dopamine levels are found in cases of Parkinson's as well, once again raising the
strange relationship LNS seems to have with this disease.

We now understand that a mistake in genetic code causes the HPRT of the LNS sufferer not to function properly and this leads to an increase in Uric acid. The lack of working HPRT during development may lead to lower levels of the neurotransmitter dopamine in the Basal ganglia of the person with LNS and this may be a cause for the neurological and behavioral symptoms of the disorder. How this abnormality of HPRT and purine metabolism might lead to a change in dopamine function remains unclear (Nyhan, 2005).

**Prevention and Treatment**

Prevention in the case of LNS is troublesome. As far as primary prevention, detecting the condition before it manifests, the one route is to genetically screen the mother. One can also measure HPRT levels in amniotic fluid to make a prenatal diagnosis. Once born, APGAR tests on LNS children often show no problems and during early childhood developmental delays are often associated with the hyperuricemia. It's not until the self-injurious behavior begins within the first year of life does one realizes they are dealing with LNS.

Secondary prevention, attempting to treat symptoms very early to perhaps overcome early delays, are also troublesome in LNS. The hyperuricemia can be treated with allopurinal but, as we have seen earlier, this does not stop the neurological and behavioral aspects of the syndrome from appearing. Spasticity can be reduced by the administration of baclofen or benzodiazepines. It has been suggested that certain anti-depressants and SSRIs (Selective Serotonin Re-uptake Inhibitors) could be useful if indeed the lack of dopamine is shown to be a primary cause of the developmental delays seen, but there is no evidence for this theory at this time. Current thought on LNS prevention is that no method of treatment for the neurobehavioral
aspects has been particularly effective, but there has been some success in trying to treat the behavioral aspect chemically as current research has shown a reduction in self-injury in LNS following S-adenosylmethionine administration (Glick N., 2006).

Sadly, most prevention and treatment options for LNS are tertiary solutions aimed at treating the symptoms. One simple step is the removal of the teeth so a person with LNS cannot bite their lips or fingers. Some dentists will not go this far with healthy teeth, even after the particulars of LNS are explained to them (Nyhan, 2005). Many people have worked on special mouthguards to allow a LNS sufferer to speak or eat but not to bite down on a finger (Luiselli et al., 1992). Korean researchers have crafted a special soft mouthguard fabricated to prevent the destruction of perioral soft tissues for LNS patients (Jeong, Lee, Kim, Kim & Tootla, 2006).

Solutions as simple as boxing gloves and oven mitts have been used to keep a person with LNS from using their hands to injure themselves and others, but many just use standard cloth restraints tied to their wheelchairs to stay under control.

One very promising avenue is the use of a procedure called Deep Brain Stimulation. Developed for Parkinson's patients some twenty years ago, recent findings lead researchers to think it might also help alleviate some of the symptoms of LNS. In 2000, a surgeon in Tokyo named Takaomi Taira used this technique to treat a nineteen year old LNS patient. The procedure involves inserting thin wires through holes in the skull until they reach a spot in the Basal ganglia called the globus pallidus. A battery is connected to the wires and the current numbs an area the size of a pea in that section of the brain. After surgery the nineteen year old male under Dr. Taira's care was vastly improved with most of his dystonic movement having disappeared completely. He was able to read comics, watch TV, and enjoy life like never before (Preston, 2007). If the electric current was discontinued the symptoms reappear though, this is
not a cure. No one is sure why this works. While very promising and worthy of more study, Dr. Nyhan is worried that invasive brain surgery on a very fragile population may do more damage than good in the long run.

The future as far as prevention and treatment of LNS is concerned also includes work with stem cells to create mutated cells with non-functional HPRT in order to analyze drugs that could be used to prevent the onset of LNS (Urbach, Schuldiner & Benvenisty, 2004), and greater understanding of brain chemistry in general, including how the brain controls different aspects of behavior (Young & Palmour, 1999).

Conclusion

As we have seen, LNS is a terrible disorder that strikes the sufferer with debilitating motor and cognitive problems, hyperuricemia and the urge to do harm to themselves and others. While we seem to have a handle on how a damaged genetic sequence leads to a defective enzyme, we are still unsure how this leads to the neurological and behavioral problems that are the hallmark of the disorder. Treatments as simple as wearing oven mitts and as complicated as electrical wiring in the brain have been used to help the LNS sufferer but no cure for the syndrome seems in sight. In the thirty-six years since Matthew was first examined by Dr. Lesch and Dr. Nyhan, much has been learned about this strangest of conditions but there is still a great deal we do not understand.
References


Luiselli J.K. Matson J.L. Singh N.N., editors (1992) Self-injurious Behavior : Analysis, Assessment, and Treatment. New York: Springer-Verlag (pp. 66-70, 96, 244-5)


