Lesch-Nyhan Syndrome: Models, Theories, and Therapies

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Key Words

Lesch-Nyhan syndrome · Models · Theories · Therapies

Abstract

Lesch-Nyhan syndrome (LNS) is a rare X-linked disorder caused by mutations in HPRT1, an important enzyme in the purine salvage pathway. Symptoms of LNS include dystonia, gout, intellectual disability, and self-mutilation. Despite having been characterized over 50 years ago, it remains unclear precisely how deficits in hypoxanthine and guanine recycling can lead to such a profound neurological phenotype. Several studies have proposed different hypotheses regarding the etiology of this disease, and several treatments have been tried in patients, though none have led to a satisfactory explanation of the disease. New technologies such as next-generation sequencing, optogenetics, genome editing, and induced pluripotent stem cells provide a unique opportunity to map the precise sequential pathways leading from genotype to phenotype.

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motor development, choreoathetosis, dystonia, crystals in the urine (later determined to be composed of uric acid), and most strikingly, self-mutilation [Lesch and Nyhan, 1964]. Upon publication of their results, other cases were recognized across the world, all in young males in an inheritance pattern consistent with an X-linked Mendelian genetic disorder [Nyhan et al., 1967]. More clues into the cause of LNS were provided by further studies by Nyhan et al. [1968] demonstrating that azathioprine treatment was unable to reduce the uric acid levels in LNS patients. This suggested that the drug was not being converted into its biologically active product in the body, a reaction catalyzed by the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). Seegmiller et al. [1967] showed that the enzymatic activity of HPRT, a protein expressed in all cells essential for purine salvage, had an activity approaching zero in the erythrocytes of LNS patients, providing a clear explanation for the inheritance pattern and hyperuricemia found in LNS. Almost 50 years later, measuring HPRT activity in erythrocytes remains the gold standard for diagnosing LNS [Nyhan, 2005].

Discovery of LNS and HPRT Deficiency

Lesch-Nyhan syndrome (LNS) was first described at John Hopkins Hospital in 1964 (fig. 1) by Michael Lesch and William Nyhan in 2 brothers with an unusual set of symptoms. Both brothers presented severe retardation of

Identification and Classification of LNS Variants

Measuring the HPRT activity of erythrocytes allowed for the identification of patients with less severe HPRT deficits, frequently in patients previously diagnosed with

Fig. 1. Schematic timeline of important milestones in the study of LNS. Studies relating to the underlying etiology of LNS, the treatment of LNS, and the generation of LNS models are highlighted in blue, red, and green, respectively.

gout or renal stone disease [Nyhan, 2005]. These patients usually had between 5–10% of normal HPRT activity and increased uric acid production, but lacked the behavioral and some or all of the neurological symptoms associated with LNS [Kelley et al., 1969]. An early exception to this pattern was a patient first described by Catel and Schmidt [1959] who had elevated levels of uric acid and many of the neurological symptoms of LNS but remained intellectually and behaviorally normal. No HPRT activity could be detected in the erythrocytes of this patient, who remained an unexplained case until the development of a radiolabeled ^{14}C HPRT activity assay by Bakay et al. [1979], which enabled the detection of low levels of nucleotide conversion in this patient. Using this technique, Page and Nyhan [1989] defined 4 distinct categories on the ‘spectrum’ of LNS, with the classic phenotype lying on one end, with almost all patients having less than 1% normal enzyme activity, and hyperuricemic individuals lacking neurological and behavioral symptoms on the other

end, with HPRT activity between 8–60% of normal. In between these 2 extremes were the patients with the ‘neurological’ phenotype, who had some or all of the neurological symptoms present in the LNS classic phenotype and had between 1.8–8% of normal HPRT1 activity [Page and Nyhan, 1989]. Finally, the authors identified one patient with the ‘intelligent’ LNS phenotype, who had all the symptoms of classic LNS, including self-mutilation, but had normal intelligence. This ‘intelligent’ LNS phenotype was defined as occurring between 1.4–1.6% of normal HPRT activity [Page and Nyhan, 1989]. However, this methodology of classifying LNS variants has fallen out of favor, as comprehensive cognition assessments of LNS patients has proven to be challenging [Nyhan, 2005]. Instead, multiple authors, including Sege-Peterson et al. [1992], Jinnah et al. [2000], and Puig et al. [2001] have proposed classifications of LNS based on variations in the motor disorder, which allowed for much less subjective criteria. Torres and Puig [2007] built upon this work and

proposed a new classification scheme for LNS classic and variant phenotypes based on behavioral, biochemical, molecular, and enzymatic data, where Lesch-Nyhan variants are segregated into 3 distinct groups of increasing severity, with LNS patients forming the fourth and most extreme category.

As knowledge of the complex interplay between genomics and metabolism grows, future analyses of LNS and its variants will no doubt continue to rely on a more integrated approach between genetic, biochemical, enzymatic, and clinical data.

Models of LNS

The Development of LNS Models

Due to the rarity of the disease (~1/380,000 live births) [Morton and Lalouel, 1977] and the inherent difficulty in acquiring human neural tissue, LNS has usually been studied by proxy, using peripheral cells from LNS patients, genetically modified neuronal cell lines, or animal models. Consequently, our understanding of LNS has grown in lockstep with the development of successive models of LNS. Due to the well-defined genetic cause of LNS, there has been a multitude of cellular and animal models of LNS produced, each with their own strengths and weaknesses, and suited for addressing different aspects of LNS.

Tissue Culture Models of LNS

The earliest models used to study LNS were based on non-neural cells that could be easily acquired from patients, mostly from blood (erythrocytes and lymphocytes) or skin (fibroblasts) [Jinnah, 2009]. These models were easy to establish and had direct relevance to the patients they were derived from. However, they cannot be used to study neurological deficits caused by a deficit in purine recycling. Therefore, these models have been primarily used to study the general biochemical consequences of HPRT deficiency [Castro Costa et al., 1980]. To circumvent this cell type problem, researchers developed HPRT-deficient subclones of glioma and neuroblastoma cell lines [Shirley et al., 2007]. These neural models have allowed researchers to assess specific deficits in neurotransmitters [Bitler and Howard, 1986; Yeh et al., 1998; Lewers et al., 2008] and neuronal structure abnormalities [Connolly et al., 2001; Shirley et al., 2007] that occur when HPRT activity is absent. However, results obtained from these models may lose relevance, as the cells were obtained from nonpatient neuronal tumors.

Despite the valuable insights that cell models have provided into the mechanisms that underlie LNS, they have limitations. Perhaps most significantly, there is no guarantee that any result obtained from cells in vitro is representative of the same cells in vivo. Thus, various in vivo models of LNS have been generated over the years, both to validate effects seen in cell models and to study the neurobehavioral phenotype of LNS.

Animal Models of HPRT Deficiency

The first animal model to be generated for LNS was an *Hprt1*-deficient mouse generated in 1987 [Doetschman et al., 1987; Hooper et al., 1987]. These mice exhibited the metabolic phenotype (e.g., increased synthesis of purines through the de novo synthesis pathway) but lacked any neurobehavioral phenotype. More recently, an *Hprt1* knockout rat model was generated, which showed similar metabolic deficits as the mouse knockout and also failed to display any neurobehavioral phenotype. As a result, these models are generally used to investigate neurochemical [Jinnah et al., 1992] and metabolic [Jinnah et al., 1993] aspects of LNS in vivo, rather than the behavioral aspects of the disease.

Animal Models of Self-Injury

Fortuitously (and serendipitously), it was discovered that rats, which were neonatally administered the dopaminergic neurotoxin 6-OHDA (6-hydroxydopamine) displayed self-injurious biting and aggressive behaviors if the metabolic precursor to dopamine, levodopa (L-DOPA), was administered in adulthood [Breese et al., 1984, 2005]. A similar dopaminergic hypersensitivity model was also created in monkeys, whereby monkeys with unilateral ventromedial tegmental lesions could be induced to bite forelimb digits and have spasticity of hindlimbs if mixed D1/D2 agonists were administered [Goldstein et al., 1986].

Purely pharmacological models have also been developed. One such model uses chronic administration of caffeine (an adenosine receptor antagonist), which induces self-injurious behavior in rats [Ferrer et al., 1982]. However, only a small percentage of rats which undergo this treatment regime display self-injurious behavior, and these tend to be mild [Devine, 2012]. A more efficacious pharmacological induction of self-injury in rats utilizes high doses of the monoamine reuptake inhibitor pemo-line [Devine, 2012]. Self-injury phenotypes were also reported in *HPRT1* knockout mice dosed with amphetamines [Jinnah et al., 1991] and may even be inducible with a single dose of clonidine, an L-type calcium channel agonist (BayK-8644) [Jinnah et al., 1999].

Each of these models detailed above presents significant challenges when relating experimental results in self-injury to LNS patients, especially because no one model is capable of reproducing all the symptoms observed in LNS. Therefore, experimental results from each model should be carefully considered in the context of what aspect of LNS the model is designed to emulate.

Theories and Therapeutics

The uniqueness of the neurobehavioral phenotype observed in LNS patients has led to many theories explaining its etiology. Currently, there is no accepted hypothesis that explains the neurobehavioral symptoms of LNS. This has made rational treatment development very difficult and has led to the absence of effective LNS treatments, despite the identification of the causal role of HPRT nearly 50 years ago. What follows is a brief review of the various hypotheses that have been put forward, the evidence for and against them, and the effectiveness of therapeutics based on these hypotheses.

Uric Acid

Shortly after the discovery of LNS, the dramatically elevated levels of uric acid in blood as a result of absent purine recycling was hypothesized to adversely influence neurodevelopment and lead to the neurobehavioral phenotype [Nyhan, 1997]. However, this hypothesis does not explain why LNS variant phenotypes (>1% enzymatic activity) that have only slightly active HPRT do not exhibit the self-injurious behavior [Bakay et al., 1979; Sege-Peterson et al., 1992]. Furthermore, patients who are prenatally diagnosed with LNS and are administered allopurinol upon birth and never have significantly elevated levels of uric acid in their blood still develop the classic LNS neurobehavioral phenotype [Jinnah, 2009], suggesting a limited role of uric acid in the neurological features of LNS. Today, uric acid overproduction is still treated using allopurinol, and while this effectively manages several aspects of the disease, including gout and liver failure, it is not thought to influence the development of the neurobehavioral symptoms of LNS [Nyhan, 2005].

Adenine

While many researchers expected that failure of purine recycling would lead to a decreased concentration of purines in LNS patient cells, HPRT deficiency appears to have little influence on purine levels in these cells [Shirley et al., 2007], as they compensate by increasing de novo

purine synthesis, exacerbating uric acid overproduction [Nyhan, 1997]. To address this, early attempts at treating LNS experimented with replenishing the purine pool. Van der Zee et al. [1970] found that administration of adenine did not improve behavioral or neurological symptoms, although it did help reduce uric acid excretion and eliminate megablastic anemia, which is observed in some LNS patients [Torres and Puig, 2007]. Another study by Ceccarelli et al. [1974] in a single patient confirmed these results and suggested that the patient may have shown some mild behavioral improvement, but the treatment had to be abandoned due to renal failure caused by the conversion of adenine into the highly insoluble compound 2,8-dioxyadenine. Further studies administering adenine did so in tandem with allopurinol to control 2,8-dioxyadenine concentration and did not observe any improvement in behavior [Watts et al., 1974]. As uric acid levels can usually be managed well using allopurinol alone [Jinnah, 2009], adenine therapy is no longer used in the treatment of LNS.

Serotonin

Several early studies suggested that LNS patients may suffer from serotonin depletion. Studies in animal models found that decreased levels of serotonin in the brain correlated with aggressive muricidal behavior, which was ameliorated by administering 5-hydroxytryptophan, the metabolic precursor to serotonin [Di Chiara et al., 1971]. This, in conjunction with findings that the serotonin catabolic product 5-hydroxyindoleacetic acid was elevated in the urine of LNS patients [Sweetman et al., 1977], prompted a clinical trial in 9 LNS patients to examine the effects of boosting serotonin. Administration of 5-hydroxytryptophan, carbidopa, and imipramine simultaneously abolished self-injury in LNS patients [Nyhan et al., 1980]. However, this effect was temporary (usually only a few weeks) and could not be recaptured at a later time point [Nyhan et al., 1980; Nyhan, 2000]. Postmortem studies on LNS brains have failed to observe any significant difference in serotonin levels in LNS patients [Lloyd et al., 1981].

Dopamine

The majority of the research into LNS has focused on dopamine, with evidence of a dopaminergic deficit strongly supported in several lines of study. Among the strongest, evidence of the clinical relevance of dopamine comes from positron emission tomography (PET) studies in LNS patients. PET studies utilizing ¹⁸F-dopa, which provides a measurement of activity of DOPA decarbox-

ylase, concluded that LNS patients have significantly decreased dopaminergic production and storage compared to control patients [Ernst et al., 1996]. Further studies, which used ^{11}C ligands that bound specifically to the dopamine transporter, found that there is a 64–75% decrease in binding to dopamine transporters in the putamen and a 50–63% decrease in ligand binding in the caudate in LNS patients compared to controls [Wong et al., 1996]. The authors concluded that these results were consistent with decreased dopaminergic neuronal density, or decreased density of dopaminergic terminals. Volumetric imaging of the caudate in LNS patients found an average caudate volume reduction of 30% in LNS patients, further suggesting a decrease in dopaminergic neurons [Wong et al., 1996]. These results are consistent with postmortem studies carried out by Lloyd et al. [1981], which compared 3 brains of LNS patients to 8 age-matched controls. The LNS patients were found to have a 10–30% decrease in levels of several biochemical markers of dopaminergic activity in the caudate, nucleus accumbens, and external palladium, including homovanillic acid, DOPA decarboxylase, tyrosine hydroxylase, and dopamine itself. HPRT-deficient subclones of neuronal-like cells are also reported to demonstrate a loss of dopaminergic activity [Lewers et al., 2008] as do HPRT-deficient mice [Jinnah et al., 1992, 1993].

Following this line of evidence, there have been several attempts to reduce the dopaminergic deficit by boosting dopamine production. To date, several small trials have supplemented LNS patients with exogenous sources of substrate needed in the dopamine synthesis pathway. One such molecule, L-DOPA, is synthesized into dopamine by DOPA decarboxylase and is widely used to increase levels of dopamine in the brain, most notably to treat Parkinson's disease [Cotzias, 1969; Lloyd et al., 1975] and general dystonia [Lubarr and Bressman, 2011].

However, the reported effectiveness of L-DOPA in LNS has been inconsistent, ranging from slightly positive to a significantly negative effect on self-mutilation and aggressive behavior. Mizuno and Yanagi [1974] administered L-DOPA as a control in a study examining serotonin replacement and its effects on aggressive behavior. The authors noted that L-DOPA had minute effects on decreasing self-mutilating behavior, and this effect was temporary and not as prominent as the serotonin treatment. While several trials have replicated this improvement [Mizuno and Yugari, 1975; Manzke et al., 1986; Jankovic et al., 1988; Serrano et al., 2008], many others have reported no improvement or worsening of patient

symptoms following administration of L-DOPA [Ciaranello et al., 1976; Castells et al., 1979; Watts et al., 1982; Silverstein et al., 1985; Jankovic et al., 1988; Hunter et al., 1996; Schneider et al., 2006; Visser et al., 2011; Rebai et al., 2014] including the exacerbation of the patient's dystonia [Watts et al., 1982] and hyperactivity [Visser et al., 2011]. The conflicting results obtained from L-DOPA treatment suggest that it is not effective for LNS and make it difficult to determine the mechanism by which L-DOPA impacts the behavior of LNS patients. As Visser et al. [2011] conclude, L-DOPA is not a reliable treatment for LNS, and other treatments must be developed to combat motor and behavioral dysfunctions of these patients.

An alternate hypothesis on the role of dopamine in LNS is that the dopaminergic deficiency results in increased sensitization of dopamine receptors in the remaining dopaminergic cells, and that this sensitization is the underlying cause of the neurobehavioral phenotypes found in LNS [Goldstein et al., 1985]. This hypothesis is consistent with behavioral models of LNS, such as 6-OHDA-lesioned rats, which appear to self-injure in response to an increase in dopaminergic production [Breese et al., 1984, 2005]. Animal studies using dopamine antagonists were able to attenuate self-injury in multiple animal models of self-harm, including 6-OHDA-lesioned rats and unilateral ventromedial tegmental lesions in monkey models [Goldstein et al., 1986; Duncan et al., 1987; Criswell et al., 1989; Allen et al., 1998; Moy et al., 2001, 2004]. Further, postmortem brains of LNS patients show increases in dopamine receptors [Saito et al., 1999], and HPRT-deficient mice are hypersensitive to dopamine-releasing agents [Jinnah et al., 1991, 1992].

Translating dopamine hypersensitivity into therapeutics for LNS patients has been difficult, with variable results. SCH-12679, a D1 receptor antagonist was investigated in non-LNS aggressive individuals [Itil et al., 1972], and its effect was hypothesized to be translatable to LNS patients, but the study was halted due to adverse effects on LNS patients [Albert et al., 1977; Elie et al., 1980]. Fluphenazine, a D1 and D2 receptor antagonist, has shown improvements in self-biting [Goldstein et al., 1985; Jankovic et al., 1988; Gualtieri and Schroeder, 1989], but the use of this drug was again discontinued because of severe side effects of akathisia and tardive dyskinesia [Gualtieri and Schroeder, 1989]. The antipsychotics haloperidol, pimozide, risperidone, and tetrabenazine primarily antagonize the D2 receptor with some D1 receptor binding. These drugs have shown variable results, improving self-mutilating behavior in some patients [Jankovic et al., 1988; Allen and Rice, 1996; Jeong et al.,

2006; Crapper and Ernst, 2015] while showing no effects in others [Watts et al., 1982; Dabrowski et al., 2005]. As these drugs have multiple targets within the central nervous system, it is unclear whether the improvement in symptoms is due to the drug's effect on the dopaminergic system or not. Recent studies of ecopipam, a selective D1 receptor antagonist, reported that several patients showed improvement in their self-injurious behavior, while others had to discontinue the trial due to adverse side effects [Khasnavis et al., 2016a, b]. However, whether the improvement in those patients who responded to ecopipam was a result of the sedative side effect of the drug or direct attenuation of self-mutilating behavior is yet to be determined. At present, there have been no reports of any dopamine antagonists that produce broadly positive outcomes in a majority of LNS patients.

Deep Brain Stimulation

Many avenues of LNS treatment development have been discovered serendipitously, rather than through rational drug design. Deep brain stimulation is a surgical treatment for hyperkinetic and hypokinetic movement disorders, performed through insertion of electrodes into the thalamus or globus pallidus where they are chronically stimulated at a high frequency [Miocinovic et al., 2013]. Taira et al. [2003] reported a case study of a 19-year-old male with LNS who underwent deep brain stimulation of bilateral globus pallidus internus (GPi) for control of dystonic movements. However, postoperative follow-ups revealed that in addition to improvement in the patient's dystonic movements, his self-mutilating behavior had disappeared completely. While Taira et al. [2003] were unable to test whether the improvement in self-mutilating behavior was a direct effect of the GPi stimulation, this finding demonstrated that pallidal deep brain stimulation may be an effective treatment for alleviating self-mutilating behaviors.

Throughout the following years, other studies were conducted to assess the efficacy of deep brain stimulation in Lesch-Nyhan patients. Cif et al. [2007] performed bilateral stimulation of antero-ventral and posterior segments of the GPi. Through separate stimulations of these regions, which are part of the limbic and motor circuits, respectively [Afifi, 1994], the authors demonstrated that stimulation of the limbic GPi attenuates aggression and self-mutilating behavior, while stimulation of the motor GPi alleviates dystonia and dyskinetic movements. This was further examined by selective discontinuation of stimulation in either of the regions, which resulted in resurgence of the self-mutilation and dystonia after sev-

eral days, showing that the improvements were a direct result of the GPi stimulation, and the motor and behavioral deficits of LNS are mediated through different circuits, both involving the GPi. Similarly, Deon et al. [2012] and Piedimonte et al. [2015] were successful in controlling patients' motor and behavioral dysfunction through bilateral stimulation of GPi using single electrodes on each side of the brain. An interesting finding was observed in a patient studied by Abel et al. [2014] when a technical problem arose. The LNS patient underwent bilateral single electrode implantation in the GPi and experienced improvement in both dystonia and self-mutilation. However, following an accidental fracture of the right electrode, the patient began experiencing dystonia and self-mutilating behavior but only on the left side of his body, which could be treated with replacement of the damaged electrode. This finding suggests that the deficits in the motor and limbic circuitries are lateralized. Deep brain stimulation efficacy in behavioral and motor improvements was maintained for at least 2 years following the implantation in a small number of patients studied to date, except for one patient who died due to an airway obstruction. These studies demonstrate that deep brain stimulation may be a promising method to treat self-mutilating behavior and dystonia associated with LNS.

Treatment with S-Adenylmethionine

Another serendipitously discovered treatment for LNS was reported by Glick [2006], who found that treating an LNS patient with S-adenylmethionine (SAM) in order to reduce transaminase levels (elevated due to regular fentanyl administration) showed an unexpected and dramatic decrease in self-injury that was persistent over several years. A less rigorous but similarly positive description was reported for a young LNS patient shortly thereafter [Dolcetta et al., 2013]. However, Dolcetta et al. [2013] conducted a study where SAM was administered to 13 LNS patients; 4 showed significant positive improvement, but the majority of patients experienced worsening of their symptoms. Chen et al. [2014] administered SAM to 5 related LNS patients and found a significant reduction of self-harm and aggressive behavior in all 5 patients. Recently, a double-blind placebo-controlled trial was conducted in a single patient by Lauber et al. [2016], where the authors found a significant decrease in self-injury when SAM was administered. While there have only been limited studies on SAM as a medication for LNS with contradictory findings, it remains a promising avenue of treatment for LNS. Of particular in-

terest is the mechanism by which SAM achieves its beneficial effect on LNS. It has been hypothesized that SAM may be replenishing the purine pool [Lauber et al., 2016], but there is currently no direct evidence of this.

New Tools to Investigate LNS

The conflicting data between many LNS models and clinical trials highlight the need for new models and new techniques for evaluating them. One promising avenue for generating a more accurate model of LNS on a cellular scale is to use induced pluripotent stem cells (iPSCs), where differentiated patient cells are induced into a pluripotent state [Takahashi et al., 2007]. These iPSCs can then be differentiated into a wide range of cell types, including many subtypes of neurons [Yamanaka, 2012], enabling the generation of patient-specific cellular models in cell types that were previously impossible to culture or difficult to acquire [Hallett et al., 2015]. To our knowledge, there are no reports of iPSCs being used to probe the etiology of LNS or to test potential therapeutics for LNS. iPSC lines have been created from an LNS carrier and patients [Park et al., 2008] but have been solely reported using HPRT presence or absence as a selectable marker to study basic stem cell functions [Mekhoubad et al., 2012]. If pursued, iPSC-based models of LNS will allow experiments to be performed on patient's genetic backgrounds in different neuronal cell types and allow for rapid gene editing with tools such as CRISPR/Cas9 to develop isogenic controls [Bell et al., submitted] or could be used as a source of functional dopaminergic neurons [Hallett et al., 2015].

CRISPR-Cas9 genome editing could also be employed to reduce the barrier to creating new animal models of LNS [Dow, 2015]. Ideally, a new animal model would mimic the self-injury behavior found in humans solely due to HPRT deficiency. However, based on the results of the mouse [Jinnah et al., 1992] and rat [Isotani et al., 2016] *Hprt1* knockout models, it is possible that self-injury due to a loss of HPRT may only occur in a CNS that is more analogous to humans than those found in rodents. Therefore, a logical step in animal modeling for LNS would be nonhuman primates, although the high costs and uncertain results of creating such a knockout [Kang et al., 2015] might outweigh the potential benefits of a new *Hprt1* knockout model.

The dopaminergic systems of existing genetic animal models could be further interrogated by using optogenetics to probe the specific dopaminergic pathways [Bass et

al., 2010]. Similarly, optogenetics could be employed in behavioral animal models to investigate if stimulation of a particular population of dopaminergic neurons would ablate or worsen self-injurious behavior [Mikhailova et al., 2016]. These studies could be modeled on previous ontogenetic-based investigations of the dopaminergic system's role in mediating aversive behavior [Danjo et al., 2014].

Both animal and cellular models could be paired with whole-genome gene expression tools such as single-cell RNA sequencing [Morris, 2016] to provide an unprecedented resolution of molecular changes that may be caused by HPRT dysfunction at different stages of development. Together, new techniques, more relevant models, and an adequate sample size might allow for a better understanding of the etiology of LNS.

Concluding Remarks

Since its first description in 1964, LNS has captured the imagination of clinicians and scientists worldwide. In the intervening 50 years, the genetic basis of the disease has been determined, the symptoms caused by overproduction of uric acid is controlled, a wealth of information about the effect of HPRT deficiency has been uncovered, and a few promising therapeutics have been tested to deal with the neurobehavioral phenotype. This is clear progress. However, for many LNS patients and their families, efficacious treatment for persistent self-mutilation remains unreachable.

In order for more effective treatment of LNS to be developed, the underlying etiology of the disease must finally be understood. Future studies should examine how treatments that have shown positive results in LNS patients, notably deep brain stimulation and SAM administration, are able to ablate or reduce self-injury. Additional trials should also be conducted for these therapies to help resolve the contrasting results obtained by different research groups. While the rarity of LNS has made obtaining sufficient numbers of subject to conduct clinical trial challenging, studies conducted by Khasnavis et al. [2016b] and Lauber et al. [2016] demonstrate how a double-blind placebo-controlled study can be employed to help generate meaningful data from a low number of subjects.

Treatments that show positive results in LNS models but fail in patients may indicate that current models of LNS do not efficiently replicate a complete biochemical picture of HPRT deficiency in the human brain. Utilizing

new modeling strategies in combination with cutting-edge investigative techniques offer the potential for a greater understanding of the etiology of LNS and more effective treatment options.

Statement of Ethics

The research of Dr. Carl Ernst has been approved by the Douglas Hospital Ethics Board.

Disclosure Statement

The authors declare no conflicts of interest.

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