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A Review on Lafora Disease

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ABSTRACT:
The neurodegenerative condition known as Lafora's disease is brought on by recessive loss-of-function mutations in the genes that encode laforin glycogen phosphataes or malin E3 ubiquitnilgase. Lafora bodies, misshapen precipitated glycogen clumps, are a hallmark of neuropathology. Patients, who were asymptomatic until puberty, develop myoclonus epilepsy that progresses slowly at first, then quickly, leading to a vegetative condition and death within ten years. The interaction between laforin and malin controls glycogen phosphorylation and chain length pattern, the latter of which is essential for glycogen solubility. The precise mechanistic knowledge is still significantly lacking. A direct current road to therapy is made possible by the discovery that a partial reduction in brain glycogen synthesis almost fully prevents the disease in its hereditary animal models.
Adolescents who were previously healthy typically develop the condition, and within ten years of symptom onset, mortality frequently happens. Loss-of-function mutations in NHLRC1 which encode laforin and malin, respectively, are the cause of lafora disease. Poorly branched, hyperphosphorylated glycogen, which precipitates, aggregates, and builds up into Lafora bodies, is the outcome of either protein's absence. Evidence from genetic mouse models of Lafora disease indicates that these intracellular inclusions are a major contributor to neurodegeneration and neurological disease. Combining current knowledge about the function of laforin-malin as an interacting complex suggests that laforin recruits malin to parts of glycogen molecules where too long glucose chains are formed to prevent chain elongation. However, the knowledge appears already adequate to advance disease course altering therapies for this catastrophic fatal disease.

KEYWORDS: myoclonus , pseudo-arylsulphatase, dementia, polyglucosans, N-acetylaspartate ,lafora bodies

I. INTRODUCTION

Lafora disease is a rare autosomal recessive and severe form of progressive myoclonus epilepsy. After onset, which usually occurs during late childhood or early adolescence, Lafora disease is invariably fatal, typically within 10 years . The condition was first described by Lafora and Glück over 100 years ago. A postmortem study showed profuse accumulation of small inclusion bodies in many tissues, including the brain. These inclusions, subsequently termed Lafora bodies, became the hallmark of the disease. They were shown to be composed primarily of abnormal glycogen4 placingLafora disease in the context of glycogen metabolism disorders.

The second known case of the around a dozen progressive myoclonus epilepsies is Laforadisease . The first case was seen by Spanish neuropathologist Gonzalo Lafora in the later half of the first decade of the 20th century when he was working close to Washington, DC, at the Government Hospital for the Insane at the time. Lafora was a student of Cajal, Alzheimer, and Kraepl. He provided such thorough descriptions of the neurological characteristics, recessive inheritance, and disease progression that they have never actually been considerably improved upon. However, Lafora did not have access to a camera. He looked over a several of the patients autopsy brains and was the first to be alarmed by the sight of several huge two-layered spherical formations that frequently took up the whole neuronal cell bodies. These brains were obviously distinct from those of the individuals whose progressive myoclonus epilepsy had any visible neuropathological correlate and who were reported by Unverricht in the closing years of the previous century. The pathology community did not start referring to the illness as Lafora's bodies until more

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than fifty years later, while Lafora was still alive.

BACKGROUND:

Report, which came before the illness could be genetically categorized, was constrained by a tiny study group size of only two patients. This research indicated that linguistic and intellectual processes were mostly preserved but praxis was primarily affected by nondominant parietal lobe function.

Another prominent trait is myoclonus.

Myoclonus that occurs suddenly Gonzalo Rodrguez-Lafora, who first reported the distinctive intracellular inclusions observed in the disorder in 1911, is the name-bearer of Lafora disease. Lafora was a Cajal pupil, and Nanduri et al. exhaustively researched his life story. Lafora recounted a family of 14 siblings in his first paper and in a subsequent one with Glueck in which one male adolescent died from an epileptic disorder.Lafora noted the appearance of amyloid bodies filling the cells and squeezing the nuclei, despite the fact that the disease had already been documented.

CLINICAL MANIFESTATION:

The disease often manifests at around 11 years of age. There have been reports of early-onset cognitive impairment variations, which are detailed here. The illness is autosomal recessive in nature and is more prevalent in cultures where consanguinity is practiced, hence the incidence varies around the world.

myoclonus, and dementia—were highlighted by Mouren and Roger. Generalized tonic-clonic An Italian study looked into the links between clinical traits and genetic phenotypes. The incidence of the many genetic variations of the disease will change in each population, as this work has shown. In the aforementioned example, the genetic variation that is less prevalent globally is the variation that is more prevalent in an Italian community. The most prevalent variety locally is also recorded less commonly worldwide in families described in Japan. It's possible that other descriptions in the literature date from before the disease was genetically classified and before we were aware of the many mutation kinds.

Even in cases when founder effects have been thoroughly discussed, the clinical phenotype, particularly the age of onset, may vary greatly. The age of onset ranged by 4 years between the earliest and latest appearance of symptoms in a family of four siblings who all had the same genetic mutation. Delayed onset may start in the third decade or later. When the illness first manifests in early adulthood, the victims may live into their fifth decade.

The three main symptoms of Lafora disease—epilepsy, seizures, myoclonus, and dementia were the index symptoms in a large group of 21 patients from 16 Indian families. Even though the individuals mentioned in the study belonged to various families, founder effects may prevent these symptoms from being universally typical. Non-convulsive status epilepticus is a rare early symptom of the illness in a previously healthy person. Other early symptoms could include headaches and academic difficulties.

Lafora disease is characterized by dementia and cognitive impairment. The frontal lobes are primarily damaged, according to a combination of research comparing the neuropsychological profile and magnetic resonance spectroscopic indices. Lower levels of parietal engagement are present. Again, because a less prevalent genetic variant of Lafora illness was overrepresented.

In this study, its generalizability may be constrained. Magnetic resonance spectroscopy investigations show abnormalities, including a decrease in N-acetylaspartate/creatinine ratios in the frontal lobes, the occipital lobes, the cerebellum, and the basal ganglia, as may be predicted of diseases with dementia and cerebellar dysfunction. Another earlier localization and spontaneously are both common. Variants like the induction of myoclonic characteristics by visual cues have been discussed. Visual impairment is one type of visual symptom. There have also been reports of other visual manifestations, such as hallucinations, which are frequently attributed to ictal discharges. Antipsychotic drugs have been shown to work well against non-epileptic visual hallucinations, though. Rarely, nystagmus is documented in conjunction with late-onset optic atrophy ; nevertheless, there was not clear histological evidence of Lafora disease in this group of patients with progressive myoclonic epilepsies. Given the typical situation of consanguinity, additional autosomal recessive concomitant disorder should be taken into consideration when uncommon clinical characteristics linked with Lafora disease, such as optic atrophy or macular degeneration, are documented.

Rarely, the disease may first emerge with extra-neurological symptoms such hepatic failure. Inadvertently observed abnormal liver function

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tests have induced liver biopsy on their own. Heart involvement is uncommon, but it has been noted in two older people with heart failure who had no other evident causes, one of whom was a 6-year-old with very early-onset dementia and an associated cardiac conduction ab-normality.

There have been reports of a very delayed clinical course of Lafora illness in people with low levels of arylsulphatase A. The significance of this is unclear, however it is possible that the genetic mutation represented a slower variety of the disorder that was also coincidentally linked to pseudo-arylsulphatase deficiency. It is also possible for arylsulphatase deficiency, another genetic disorder, to coexist with Lafora disease.

Intercurrent problems lead to mortality after the growth of polyglucosan. Then, Laforin controls a mechanism of negative feedback to suppress glycogen synthase. Another procedure that similarly facilitates the elimination of glycogen synthase involves malin and laforin. When these processes go wrong, polyglucosan builds up and the distinctive inclusion bodies of Lafora disease emerge.

Amylolytic enzymes can break down glucose polymers called polyglucosans. Lafora bodies are comparable to corpora amylacea in this regard. Lafora bodies have been found to be most prevalent in layers III and V of the cortex during autopsies, and abnormalities in the pyramidal cells of these same layers have also been observed.

The sensory and motor cortices in Lafora illness are hypoexcitable in response to afferent stimuli, according to EEG studies contrasting the condition with Unverricht-Lundborg disease, another form of progressive myoclonic epilepsy. Unknown factors cause the cortex's inhibitory control to be compromised, which leads to seizures. It is well known that these two disorders have quite different electrical characteristics. Unverricht-Lundborg disease exhibits early facilitation when looking at how afferent sensory inputs affect motor evoked potentials, whereas Lafora disease exhibits delayed and prolonged facilitation. According to positron emission tomography, Lafora illness is linked to decreased cerebral blood flow, cortical glucose metabolic rate, and oxygen metabolic rate.

DIAGNOSTICS:

An appropriate history and physical examination should provide indicators that Lafora illness may be present. It is highlighted how crucial it is to investigate the family history of consanguinity. In a review, Minassian discusses the prolonged neurological decline. Lafora illness is known to cause abrupt unexpected death in epilepsy, as is the case with all refractory epilepsies. Even though magnetic resonance imaging scans typically do not indicate volume changes in the brain, necropsy performed after death may reveal hemispheres that have uniformly atrophied.

PATHOPHYSIOLOGY:

The cases of Lafora illness that have been genetically verified are caused by mutations in two different genes. The aberrant production of laforin or malin, two different proteins, is what causes the disorder. Laforin has been shown to be a glycogen phosphatase that is formed in response clinical differential diagnosis. Consideration and suitable research should be given to juvenile myoclonic epilepsy. Other progressive myoclonic epilepsies, measles, subacutesclerosing panencephalitics, neuronal ceriodlipofuscinoses, and secondary structural epilepsies as well. It is mandatory to undertake EEG and MRI, the two primary non- invasive investigations used to diagnose epilepsies, but as will be discussed below, they are not likely to provide a definitive answer. But the intricacies that were explained in both modalities might be useful.

TREATMENT:

Currently, AEDs are the only available treatments that control the severity and frequency of seizures and myoclonus to some degree in patients with Lafora disease. Medications include topiramate, ethosuximide, phenobarbital, zonisamide, felbamate and benzodiazepines. Most recently, perampanel, a new α-amino3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonist AED, was shown to be effective in two single-case studies and a group of ten patients. The ketogenic diet was also tried in a group of patients with relatively advanced disease but was shown to be ineffective. This finding was surprising given that the diet converts brain energy usage from glucose to fatty acids, thus presumably reducing the neuronal glucose availability for glycogen synthesis. Unpublished work from our laboratory did show the effectiveness of this diet in a Lafora disease mouse model, and the possibility remains that the failure in the clinical setting was attributable to the overly advanced disease in the treated patients rather than to actual ineffectiveness.

In mice and rats, metformin was shown to

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have positive effects on neuronal survival and seizure termination. Studies in a mouse model of Lafora disease showed that metformin ameliorated neuropathological symptoms, reduced seizure susceptibility and slightly reduced the numbers of Lafora bodies. No clinical data are yet available regarding the efficacy of metformin as a treatment for Lafora disease.

The dietary supplement sodium selenate has been shown to reduce neurodegeneration, gliosis, seizure susceptibility and memory loss in a mouse model of Lafora disease. However, a gradual decline in overall motor conditioning following an initial improvement in the treated mice raised doubts about the efficacy of the drug as a potential treatment for Lafora disease.

Aminoglycoside antibiotics, such as gentamicin, can suppress translation termination at premature termination codons and could be repositioned for potential use in patients with Lafora disease who have nonsense mutations and the use of aminoglycosides is also limited by adverse effects.

No preclinical data are available for the use of gentamicin to treat Lafora disease. Lafora disease, zonisamide had an excellent effect in controlling generalized tonic-clonic seizures and myoclonus for 2.5 years before failing. The individual then required extremely high doses of phenobarbitone to avoid convulsive status epilepticus.

Benzodiazepines often must be introduced as add-on therapy.In advanced Lafora disease, a subcutaneous midazolam infusion has been described with good effect. The dosage used in this instance ranged from 10 mg in 24 hours to 15 mg in 24 hours eventually being required.

FEATURE MOLECULES:

Currently, managing the intensity and frequency of seizures and myoclonus is the cornerstone of treatment for LD patients. The only therapy available are antiepileptic medications [13, 80]. Patients still lack targeted or curative therapy for the illness, despite modest progress in understanding the disease mechanism. Gene therapy has significantly advanced the development of medicines for hereditary diseases and gives great promise for those suffering from crippling genetic conditions. Since only two genes (EPM2A or EPM2B) are implicated in LD, gene replacement therapy is a promising treatment option for the condition. To make up for the deficit, the functioning copy of the mutant gene might be given. Apart from gene replacement therapies, other therapeutic strategies being explored for LD include degrading LBs and down regulating glycogen synthesis by focusing on GS at the DNA, RNA, or protein level. Furthermore, in addition to these more focused methods, other dietary adjustments that are already available could be employed. Israelian et al. have demonstrated in a mouse model of LD that the ketogenic diet can lessen aberrant glycogen buildup. They recommended starting the diet as soon as LD is diagnosed, ideally through a globally coordinated clinical trial to elucidate the specific function of the diet in patients.

PREVENTION:

1. Gene replacement therapy:

EPM2A or EPM2B cDNA can be used in LD to replace the missing proteins. Numerous delivery systems, such as viruses, viral-like particles, gold particles, nanoparticles, exosomes, and liposomes, can accomplish this. As of right now, CNS-directed gene replacement therapies' most effective and secure gene delivery methods are AdenoAssociated Viruses. This is largely due to the non-pathogenic nature of AAVs, transduction efficiency, and long-term transgene expression, with low-frequency transgene incorporation into the host genome.

Packaging capacity is a limitation for many diseases, and EPM2A cDNAs are less than the size limit of EPM2B. However, despite the many benefits, there are two major challenges to treating CNS disorders using AAVs. First, the blood- brain barrier (BBB) restricts the number of circulating AAV particles that transduce brain parenchyma when administered intravenously. One approach to circumventing the BBB is by injecting virus directly into CSF. Different routes of intraCSF injections, such as intrathecal administration are currently being studied in clinical gene therapy studies. IntraCSF injections may have some advantages over systemic injections. For example, delivery via the CSF may avoid the loss of virus due to pre-existing neutralizing antibodies and avoid the accumulation of off-target viruses in tissues such as the liver or kidney. In addition, the amount of virus required for intraCSF injections may be lower than that of systemic injections, resulting in fewer systemic side effects.The second field of research is the development of novel viral capsids, which can cross the BBB more effectively and distribute more widely in the brain . While novel capsids are in

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development, one naturally-occurring AAV serotype (AAV9) is capable of crossing the blood-brain barrier (BBB) in large quantities and transducing into the brain (LD). This is the current vector of choice in the field of CNS directed gene therapy. For instance, an AAV9-based capsid is used in the recently-approved FDA-approved SMA (Spinal Muscular Atrophy) gene replacement therapy (CNS-DRAT). The third major obstacle in the treatment of diseases that affect the majority of the brain (LD) is the transduction efficiency. In LD, virtually all cells in the brain are diseased, and abnormal Lymphoblasts (LBs) are produced throughout the brain (LDL). Wide-spread CNS transduction is therefore necessary. For this issue, viral capsid engineering offers hope. Even with the earliest direct intra-CSF injections, transduction effectiveness is now limited despite scientific breakthroughs in virus capsid engineering. In addition to capsid engineering, novel approaches to control the blood-brain barrier are being studied, with encouraging preclinical outcomes being achieved with focused ultrasound. These novel techniques are widely employed in clinical practice and are thought to be reasonably safe. Together with other methods, they could be utilized to used in conjunction with other techniques to improve viral transduction efficiency and boost the effectiveness of gene treatments for LD. Early intervention is always essential to stop neurodegeneration and stop severe, permanent CNS damage, once an appropriate plan has been determined.

2. Degradation of Lafora bodies:

The breakdown of accumulating LBs is another treatment focus for improving LD. In mouse models, LBs are the primary cause of the disease pathology, and their removal restores the neurological phenotype. Introducing the enzyme amylase, which breaks down polyglucans, into the brain is one method of accomplishing this. The Gentry group created an antibody- enzyme fusion (VAL-0417) recently by fusing pancreatic a-amylase to a portion of an antibody that penetrates cells and breaks down LBs. They demonstrated that in a mouse model of LD, this antibody-enzyme fusion decreased LBs in vivo and destroyed them invitro. They also showed that VAL-0417 counteracts the physiological impacts of LB buildup. This medication, an example of precision treatment, has the potential to offer LD patients a substantial clinical benefit, despite the fact that its effects have only been studied in a mouse model.

3. Reducing brain glycogen synthesis:

Lowering the synthesis of brain glycogen is one of the most promising treatment approaches for LD. In LD animal models, partial or complete deletion of the GS enzyme preserved the neurological phenotype by preventing LB production. These results led to the theory that blocking the synthesis of glycogen could prevent LD. Furthermore, research has demonstrated that a 50% reduction in GS activity may be enough to stop the disease's progression . Targets of GS include the DNA, RNA, and protein levels. The most promising instrument for DNA level modifications is the CRISPR-Cas9 system, which has significantly streamlined this process and is presently being studied in clinical trials .Using double-stranded DNA breaks (DSBs) to delete a target gene is a popular technique for CRISPR-Cas9. Non-homologous end-joining (NHEJ) repairs these double-strand breaks (DSBs) in post-mitotic cells, such as neurons, resulting in the permanent creation of indel and non-functional proteins. By specifically targeting and deactivating the brain-expressed GS isoform (GYS1), this knockout method can be used to treat LD. Regarding gene replacement therapy, AAV-mediated delivery to the central nervous system will be necessary for effective and extensive editing using CRISPR-Cas9-mediated therapy. Indeed, we demonstrated in our most recent work that AAV-SaCas9 reduces neuro inflammation and LB accumulation in LD animal models. The CRISPR-Cas9 technology has significant drawbacks despite its usefulness, such as immunological response to bacterial Cas9 protein and off-target effects. One of the most active areas of gene therapy research at the moment is optimizing the CRISPR-Cas9 system for human in vivo applications. Targeting GS at the mRNA level can be accomplished by oligonucleotide-based therapies or other RNA interference (RNAi) techniques supplied by virus. These medications belong to a newly developed class that allows for effective and powerful gene expression control. Recent years have seen tremendous advancements with these techniques. Targeting RNAs implicated in a variety of disorders, including neurological diseases, numerous candidates are presently undergoing clinical studies; some have even received FDA approval. Among these are short synthetic nucleic acids called antisense oligonucleotides (ASOs), which have undergone chemical modification in order to bind to target mRNA and cause its destruction. Gys1-ASO was recently employed in one of our trials to stop young

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mice from developing LB. Furthermore, in earlier LD mice models, the treatment prevented additional buildup of LB. Similar in function, RNAi techniques degrade RNA through distinct processes that work in tandem with other enzymes to activate ribonucleases, precisely targeting certain sequences and post- transcriptionally. Short artificial RNAs, such as divalent-siRNAs (di-siRNA), microRNAs (miRNAs), and short hairpin RNAs (shRNAs), can be used to transport these kinds of RNAi. Every one of these approaches has its benefits and drawbacks. While frequent injection is necessary to maintain therapeutic levels, ASOs do not require viral transmission. Once in a lifetime, virally transmitted miRNAs are injected, but their use is restricted to borders associated with viruses. Recent developments in divalent-siRNAs hold great promise in this area, as they still do not require viral or other delivery vehicles and have significantly longer half-lives and better transduction efficiencies than ASOs. On the other hand, since divalent-siRNA technology is young, not much research has been done on its formulations, clinical efficacy, or adverse effects. All things considered, targeting the mRNA encoding GS in the brain with any of the aforementioned.

4. Small-molecule therapies and repurposing drugs:

A smaller-molecule treatment is one of the more conventional methods for treating LD. Small molecules may influence the metabolic pathways that result in aberrant glycogen buildup, even though they cannot completely replace the gene-level action of laforin or malin. In order to treat adult polyglucosan body disease, a brain glycogenosis, a high-throughput screening test has recently been designed to find small compounds that limit GS activity. This assay may also be useful in treating LD. If administered as a digestible pill, small-molecule treatment could provide patients the least invasive and most economical choice despite numerous obstacles in its development. Re-purposing existing available medications to target LD at a pathophysiological level is another potential and simpler strategy to treating LD, in addition to searching for new small molecules. Using this method, the Sanz group demonstrated that metformin treatment decreased seizure susceptibility in an LD mice model and decreased the accumulation of LBs and polyubiquitin-protein aggregates. The European Medicines Agency designated metformin as an orphan drug for the treatment of LD based on the findings of this study. Although metformin was safe in a limited group of patients with LD, the exact clinical result is still unknown. Using a similar methodology, Molla et al. recently looked at the anti- inflammatory qualities of propranolol and epigallocatechingallate (EGCG) as possible treatments in an LD mice model. Their research also emphasizes the potential therapeutic efficacy of inflammatory modulators as cutting-edge remedies for Lafora disease.

II. CONCLUSION:

LD is an orphan disease whose fundamental mechanism is largely unclear. Because of this, the illness offers fundamental scientists a rare chance to investigate a variety of molecular processes, including as glycogen biology, protein ubiquitination, neuro inflammation, neurodegeneration, and epilepsy. These investigations will reveal significant, as yet unidentified brain and extracellular systems. For instance, research on LD has revealed that malin plays a part in small cell lung cancer. Ultimately, there are a plethora of potential treatment methods for LD, including disease gene replacement and intervention in the biochemical illness pathway that has already been identified. Developments in this and other uncommon illnesses also pave the way for the development of treatmentsfor more prevalent and complicated brain disorders.

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