ISSN No:-2456-2165

Accumulation of Lewy Bodies and Neurodegenerative Disorders: A Review

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Abstract:- Neurogenerative diseases are a few of the major causes behind degradation to human health and well-being. Diseases like Alzheimer's and Parkinson's are the major life threatening diseases that result in short lifespan and eventually death. Scientists have been trying their level best to figure out the potential causes of these diseases individually and have deciphered several approaches to cure the same. The long disputed role of Lewy bodies in causing neurodegenerative diseases is poorly understood which stands as the main hurdle in developing such neuroprotective therapies, since there has been a lot of evidence suggesting accumulation of Lewy bodies as causing these diseases. However, experts have failed to develop a preventive and a permanent approach to address these disorders. Since there is a lot of overlap in the symptom spectrum of these disorders, this review paper addresses the role of Lewy bodies in generating the same- thereby, providing a framework for permanent and preventive cure.

I. INTRODUCTION

As of a 2021 report, the Alzheimer's Disease Association estimates that the number of Americans with Alzheimer's disease could be as many as 6.2 million. An estimated 1.2 million people in the United States could be living with Parkinson's disease by 2030. Neurodegenerative diseases occur when nerve cells in the brain or peripheral nervous system lose function over time and ultimately die. Although treatments may help relieve some of the physical or mental symptoms associated with neurodegenerative diseases, there is currently no way to slow disease progression and no known cures. The causes of the diseases are also variable- genetic or environmental (toxins, supplements etc.) There has been much research on the causes of development of such disorders and all of that has boiled down to the accumulation of Lewy bodies. Therefore, a treatment that is effective in curing the major cause of the disorders-Lewy bodies- as established by research, should be able to cure these neurogenerative diseases. This review paper emphasises upon the causes of development of such Lewy bodies in the brain- both genetic and environmental, their role into development of these neurodegenerative disorders and impact, and the already established treatment so that a uniform scientific approach targeting these Lewy bodies can be developed as means to cure these diseases.

II. ABOUT LEWY BODIES

Lewy bodies are intraneuronal protein structures- aggregates of alpha synuclein. It is a protein that is encoded, in humans, by the SNCA gene and is majorly responsible for synaptic dysfunction. Its another conformation called protofibrils bears the deadliest effect on cellular homeostasis, and neuronal death. It is responsible for neurotransmitter release as it is majorly present in the presynaptic terminals of neuron cells in human brain. The presence and quantity of Lewy bodies in the different parts of the brain determines the disease it results in. In patients with Parkinson's disease (PD), Lewy bodies are found in the nigrostriatal neurons. In patients with Lewy body dementia (LBD) or dementia with Lewy bodies, Lewy bodies are widely distributed in various parts of the human brain. The impact of Lewy body accumulation in human brain in the case of Parkinson's Disease(PD) and Lewy body Dementia(LBD) has led to the classification of these neurogenetic disorders under synucleinopathies- those primarily arising from intracytoplasmic accumulation of alpha synuclein. The current research involving brain scans of Alzheimer probands also suggests presence of Lewy bodies in their neuropathological spectrum: generating a common point between Alzheimer's Disease(AD) and Parkinson's Disease(PD).

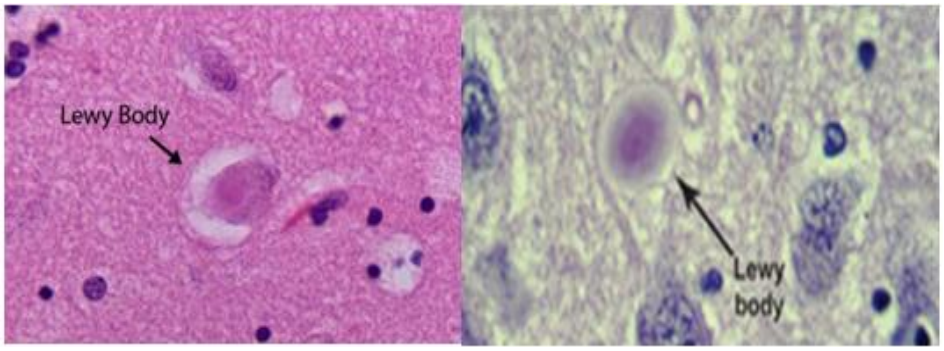

Figure 1. The figure represents Lewy bodies comprising the alpha synuclein protein.

ISSN No:-2456-2165

Postmortem autopsy was performed on dead bodies to obtain the structures and record the cause of death. A classical Lewy body is an eosinophilic cytoplasmic inclusion consisting of a dense core surrounded by a halo of 10-nm-wide radiating fibrils, the primary structural component of which is alpha-synuclein.

III. LEWY BODY ACCUMULATION: HOW AND WHERE

The process of Lewy body development has always been elusive, but experts have tried to understand the alpha synuclein fibrillization that leads to neurodegeneration. When electron microscopy (EM) was used, it clearly demonstrated that the α-synuclein inclusions do not share the compositional complexity and morphological features of the Lewy Bodies(LBs). There were variable classifications given to LBs as the results of several autopsies- dense core with irradiating filaments (classical brainstem type LB) or fibrillary structure without a central core, p62, ubiquitin (ub), and phosphorylated α-syn (pS129) immunoreactivity, and the presence of membranous organelles. In research from Mahul-Mellier et al. (4974), the researchers were eventually able to observe the transition from fibrils to α-syn–rich inclusions that recapitulate the biochemical, morphological, and structural features of the bona fide human LBs, including the recruitment of membranous organelles and accumulation of phosphorylated and C-terminally truncated α-syn aggregates which was previously not known by the models established. In the same research, the model of Lee and coworkers on cellular seeding was tested using Syn mouse PFFs , which were added to primary neuronal cultures. Immunocytochemistry (ICC) combined with high-content imaging analysis (HCA) showed that the number of filamentous aggregates continued to significantly increase in neurites but also in the neuronal cell bodies in the vicinity of the nucleus and assembled into structures similar to the morphologies of Lewy Bodies or LBs. The same research reported heterogeneous structures present in the Lewy bodies which were previously labelled and classified homogeneous by previous researches. It also recorded the changes until day 21 than previous researches that had till day 14 and discovered morphological similarities to actual LB structures- alpha synuclein aggregates had grown to resemble the structures simulated by syn mouse PFFs. The research majorly reported that the changes began in the neuronal extensions and then got transported to the perinuclear region and then modelled into LB like inclusions at a later period of time. Now, depending on where the Lewy body accumulations take place, the diseases are characterised. They accumulate in the brainstem that results in sleep disorders, constipation and depression, substantia nigra that results into tremors, slowness and stiffness and cortex of the brain that can lead to cognitive dysfunction or visual hallucinations. In the case of Parkinson's and Lewy body dementia, LBs can develop in all the three areas aforestated. Currently, the medical community is focusing on how quickly the bodies develop and in what region in contrast to the movement issues. The field develops a general conclusion for all the diseases as falling along a continuum of Lewy body disorders. In research from Sathiyamoorthy (2014), proteins that interact with LRRK2- the most commonly mutated gene associated with Parkinson's- are associated with several pathological pathways that could be targeted in the development of new therapies. Carriers of LRRK2 mutation display a varied neuropathology, including α-synuclein and tau inclusions, suggesting a vital role for LRRK2 in protein aggregation. As reported by the same research, another gene-PARK2, which is an E3 ubiquitin ligase and is involved in the degradation of misfolded or damaged proteins by the Ubiquitin-Proteasome Pathway, results in typical LBs or nigral degeneration signalling another possibility of a gene developing into Parkinson's Disease or PD. It has been confirmed that dopaminergic neurons degenerate in α-synuclein transgenic animals, thus confirming that animal models are feasible to study the formation of LBs which could enhances the chances of development of cure for these diseases by targeting the mutant genes and the pathways that lead to their development in animal models. Also, the toxicity of the Lewy body accumulation is dependent on the frequency of accumulation. Mutations in α-synuclein reduce the number of vesicles available for dopamine storage, which results in an abundance of neurotoxic by-products such as dopamine-quinone, superoxide radicals and hydrogen peroxide, and an increased level of oxidative stress- which can further lead to PD. This means that the major causes of LB development include mutations in the alpha synuclein gene, mitochondrial dysfunction(as established by previous studies) and environmental factors(influence of toxins that stimulate aggregation), and protofibrils(resulting in the death of neurons carrying out major functions of the human system).

IV. RELATION TO MAJOR NEURODEGENERATIVE DISORDERS

In Parkinson's disease or PD, there is prevalent degeneration of nigro-striatal Dopamine neurons (DA) along with rigidity, postural instability, tremor at rest and slowness or absence of voluntary movement, and neuropsychiatric symptoms. There is also less dopamine production in striatum because of the degeneration of neurons in the Substantianigra (SNc) region. Some theories about mitochondrial dysfunction, oxidative stress and impairment of ubiquitin proteosome pathway have been hypothesised but the exact mechanism of development remains unknown. The main hypothesis about development of PD that has been in focus for quite some time is the possibility of occurrence of autosomal mutations, duplication and triplication of the alpha synuclein genes which are responsible for the onset of PD. Due to the overlap of symptoms between LBD or Lewy Body dementia and Parkinson's Disease, it sometimes becomes tough for clinical diagnosis of the same. However, LBD is majorly characterised by the presence of ubiquitin in neurons alongside Lewy bodies. It leads to changes in alertness and attention, confusion, loss of memory, inability to movie smoothly and rigidity. Focus has been to not use antipsychotic therapy to cure the diseases because it leads to neuroleptic sensitivity, therefore shift has been made to the usage of pharmacological agents.

ISSN No:-2456-2165

In research from NHS UK website, Alzheimer's disease(AD) is thought to be caused by the abnormal build-up of proteins(including alpha synuclein) in and around brain cells. One of the proteins involved is called amyloid, deposits of which form plaques around brain cells. The other protein is called tau, deposits of which form tangles within brain cells. There has also been observed the presence of Lewy bodies in the autopsy of AD probands which form a common point of linkage between AD and PD diagnosis. In Alzheimer's disease, as brain cells become affected, there's also a decrease in neurotransmitters involved in sending messages, or signals, between brain cells. Levels of one neurotransmitter, acetylcholine, are particularly low in the brains of people with Alzheimer's disease. Memory loss and inability to realise the presence of the surroundings are few of the major symptoms affecting Alzheimer patients. Since previous research has notified the impact of Lewy body accumulation on the levels of various dopamine transmitters due to the deposit of the same in related areas of the brain, the symptoms portrayed by these neurodegenerative disorders can be due to the accumulation of LBs. The research also highlights the effect of the same on the major body functions depending on the location of the deposition. The emphasis needs to be directed towards preventing the accumulation of these bodies which affect major body functioning and mental stability by disrupting human homeostasis.

V. PRESCRIBED TREATMENT

There is no prescribed treatment for Lewy Body dementia or LBD but the treatment granted after diagnosis is based on the specific effect of Lewy body accumulation. Therefore, the medications prescribed overlap with those of Alzheimer's Disease(AD) and Parkinson's Disease(PD) majorly depending on the symptoms that develop in the human body. Alzheimer's disease medications, such as rivastigmine (Exelon), donepezil (Aricept) and galantamine (Razadyne) which work by increasing the levels of neurotransmitters, also improve alertness and cognition and reduce hallucinations are given to patients with LBD diagnosis apart from Alzheimer's. Medications, such as carbidopa-levodopa (Sinemet, Rytary, Duopa) which help reduce parkinsonian signs and symptoms, such as rigid muscles and slow movement are also prescribed to those patients that develop Parkinson symptoms. Occupational and Speech therapies are also given to patients with Lewy Body Dementia(LBD) to help improve their lifetsyle. Apart from Cholinesterase inhibitors like rivastigmine (Exelon), donepezil (Aricept) and galantamine (Razadyne) that are also prescribed to LBD probands, treatment of Alzheminer's also involves Memantine- a drug that works in another brain cell communication network and slows the progression of symptoms with moderate to severe Alzheimer's disease. In June 2021, the Food and Drug Administration (FDA) approved aducanumab (Aduhelm) for the treatment of some cases of Alzheimer's disease. This is the first drug approved in the United States to treat the underlying cause of Alzheimer's by targeting and removing amyloid plaques in the brain. For treating Parkinson's disease, medications like Levodopa, Inbrija and Duopa are prescribed to patients that help increase dopamine levels. Several anticholinergic medications are available, including benztropine (Cogentin) or trihexyphenidyl to help control the tremor associated with Parkinson's disease. Doctors may also prescribe amantadine alone to provide short-term relief of symptoms of mild, early-stage Parkinson's disease. Surgical procedures like deep brain stimulation are also performed which implant electrodes into specific parts of the brain that send electrical pulses to the brain to control the symptoms developed as a result of Parkinson's. The idea is to find a plausible overlap in the treatments assigned to the diagnosis of these disorders in order to develop a uniform approach for cure. But to prevent the disorders from developing in humans, we need to trace the genetic grounds on which their lies a possibility of occurrence, and other environmental stimulants that may accelerate the growth. This will require establishing a treatment that is able to prevent Lewy body accumulation in significant areas of the brain that result into cognitive dysfunction, low levels of neuro transmitters, and dementia.

VI. CONCLUSIONS

The major research that has been conducted to understand the accumulation of Lewy bodies has concluded its development to the aggregation of alpha synuclein protein. Therefore, therapies that prevent this aggregation are extremely essential. More research needs to be conducted to understand the manifestation of early symptoms of alpha synuclein protein aggregation in the brain which can provide room for such therapies that target such accumulation. Since animal models have proven to be an effective source to understand the development of such neurodegenerative diseases, gene therapy can be performed to replace those mutant genes like LRRK2 and PARK2 that accelerate protein aggregation- tau and alpha synuclein. The defective genes can be identified by the genetic testing of the individual at an early stage- embryonic or adolescent so that therapy can be conducted. This can be enhanced by tracing the family history of the concerned individual and identifying potential neurodegenerative diseases. Since prevention of alpha synuclein protein accumulation is associated with healthy neuronal functioning and healthy balance of dopamine levels, therefore, the focus should be to degrade or possibly prevent this accumulation. Neural stem cell therapies with insertion of accurate immunosuppressor genes can also be tried to replace the degraded parts after testing on a sample animal model. The research needs to focus on a fair clinical diagnosis of such disorders due to the extravagant overlap of prevailing symptoms and a treatment approach that is both able to maintain neurotransmitter levels and degrade alpha synuclein accumulation. Even if such a therapy is devised once, the broader idea should also be to prevent the accumulation of such aggregates in the future.

REFERENCES

[1]. Aschner, Michael, and Lucio Costa. *Environmental Factors in Neurodevelopmental and Neurodegenerative Disorders*. 1st ed., Academic Press, 2015.
[2]. Gilbert, Rebecca. "Lewy Bodies, Dementia, and Parkinson's – What Does It All Mean?" *APDA*, 24 May 2021, www.apdaparkinson.org/article/understanding-parkinsons-disease-dementia-lewy-bodies.
[3]. "Lewy Body Dementia - Diagnosis and Treatment - Mayo Clinic." *Mayo Clinic*, 8 June 2021, www.mayoclinic.org/diseases-conditions/lewy-body-dementia/diagnosis-treatment/drc-20352030.
[4]. LIU, H. "Alpha-Synuclein and Parkinson Disease." *Neural Regeneration Research*, vol. 2, no. 4, 2007, pp. 239–43. *Crossref*, doi:10.1016/s1673-5374(07)60053-x.
[5]. Mahul-Mellier, Anne-Laure, et al. "The Process of Lewy Body Formation, Rather than Simply α-Synuclein Fibrillization, Is One of the Major Drivers of Neurodegeneration." *Proceedings of the National Academy of Sciences*, vol. 117, no. 9, 2020, pp. 4971–82. *Crossref*, doi:10.1073/pnas.1913904117.
[6]. NHS website. "Diagnosis." *Nhs.Uk*, 14 July 2021, www.nhs.uk/conditions/alzheimers-disease/diagnosis.