


Significance of Lewy Body Formation in Development of Parkinson's Disease

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ABSTRACT

Parkinson's disease is a serious neurodegenerative disease characterized by depletion of neurons in the substantia nigra of the basal ganglia. These dying out neurons are found to contain traces of Lewy bodies, an abnormal protein filament of alpha-synuclein and that otherwise play an important role in the nervous system, especially at synapses.

Keywords: Alpha-synuclein, Lewy bodies, parkinson

ABSTRAK

Penyakit Parkinson merupakan penyakit neurodegeneratif serius ditandai dengan deplesi neuron di substansia nigra ganglia basalis. Neuron ditemukan mengandung jejak *Lewy Bodies*, yang merupakan filamen protein abnormal *alpha-synuclein*. **Shivanki Sahay, Dias Rima Sutiono. Peranan *Lewy Body* dalam Perkembangan Penyakit Parkinson**

Kata kunci: Alpha-synuclein, Lewy bodies, parkinson

INTRODUCTION

Parkinson's disease affects more than 10 million people globally,[1] about 5% cases is inherited.[1] It is characterized by the degeneration of dopaminergic neurons in substantia nigra. Diagnosis is based on the clinical history and physical examination; no specific laboratory test can confirm the diagnosis. Due to this, diagnosis is almost never done in the early stages of its development.[1,2]

Lewy Bodies are abnormal protein aggregates made up mainly of alpha-synuclein and appear as eosinophilic cytoplasmic inclusion. They are commonly manifested in patients with Parkinson's disease and those with Lewy Body Dementia, both of which share a range of clinical and morphological features. These two are classified under the umbrella term for Lewy Body Diseases.[3,4]

This review highlights the development of Parkinson's disease itself and how Lewy Bodies play an important role in the diagnosis and development of the disease.

Pathophysiology, Symptoms, and Diagnosis of Parkinson's Disease

Parkinson disease's main neuropathological feature involves the slow, progressive death of pigmented dopaminergic cells from the zona compacta of the substantia nigra; it is mostly detected in patients around sixty years of age.[2-4] This subsequently results in depletion of dopamine in the striatum. It is believed to result primarily from abnormalities in the functioning of the basal ganglia.

To understand the pathophysiology of Parksinson's Disease, the anatomy and physiology of the basal ganglia must be first understood. It consists of a range of components (**Figure 1**):[5,6]

1. *Neostriatum* consisting of the caudate nucleus and putamen
2. External and internal *pallidal segments* (GPe and GPi)
3. *Subthalamic nucleus* (STN)
4. *Substantia nigra* with its pars reticulate and pars compacta (SNc)

These parts work both anatomically and physiologically in two segregated loops:[6]

1. *Cortical areas* that can be motor, associative or limbic depending on the function of the concerned part

2. *Thalamic areas* whose components form a circuit largely separate from ones involved in cerebellar outflow pathways

This loop originates in the precentral motor regions of GPe, GPi, SNr and STN, VA/VL. They send efferent signals back to the putamen with their target being the direct pathway as well as cholinergic striatal interneurons.[6] Glutamatergic afferents from specific areas of the cerebral cortex or thalamus are sent to the striatum and STN. They transfer this information to the basal ganglia output nuclei, GPi and SNr. Furthermore, there are projections between the striatum and GPi/SNr, which are further of two types; direct and indirect.[6] The direct pathway involves a monosynaptic connection while the indirect pathway occurs via intercalated GPe and STN. Their resulting outputs mainly go to the ventral anterior and ventrolateral nuclei of the thalamus (VA/VL). These in turn project back to the cerebral cortex. [6] These projections, originating

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from the basal ganglia are found in lesser quantities in the intralaminarcentromedian and parafascicular thalamic nuclei (CM/Pf) and brainstem structures such as the superior colliculus, pedunculopontine nucleus (PPN) and the reticular formation. [6]

On the other hand, the striatum also receives prominent dopaminergic inputs from the SNc. The dendritic necks of the spiny output neurons (MSNs) are host to the termination points of the nigrostriatal projections as well as corticostriatal terminations. Dopaminergic inputs are anatomically placed in a way so as to regulate this corticostriatal transmission. Parts of MSNs in the direct pathway carry dopamine D1-receptors and those in the indirect pathway carry D2 receptors.[6] Dopamine secreted from the nigrostriatal projections seem to facilitate transmission at corticostriatal synapses onto the direct pathway of MSN and also to reduce transmission along its indirect pathway. Its net action may hence be to minimize GPi/SNr activity, which in turn facilitates activity in thalamocortical projection neurons as well as to facilitate movement through better activation of the cerebral cortex.[6]

Simply put, the basal ganglia consist of a complicated network of deep nuclei with the putamen, caudate, globus pallidum, and substantia nigra involved in the integration of motor and sensory inputs.

The cerebral cortex itself is a thin, gray covering of both hemispheres of the brain and has four main functional areas. The basic functions of these individual lobes are as follows:[9, 10]

1. Frontal Lobe: reasoning, planning, certain parts of speech, movement, emotions and problem solving
2. Parietal Lobe: movement, orientation, recognition, perception of stimuli
3. Occipital lobe: visual processing
4. Temporal lobe: perception and recognition of auditory stimuli, memory and speech
5. Parkinson's disease mostly results in a crippling impairment of voluntary movement. The commonly observed clinical manifestations in such patients are:[2, 11, 12]
6. *Tremor or shaking* in fingers, thumbs, hands, chin or lips as well as twitching or shaking of limbs
7. *Small handwriting*; mainly a sudden decrease in handwriting characterized by decrease in letter size and words coming closer
8. *Trouble sleeping*, characterized by sudden movements in bed such as uncontrollable actions like kicking or punching in sleep, or falling off the bed
9. *Loss of smell*
10. *Trouble moving or walking,* characterized by stiffness or pain in shoulder and hips
11. *Constipation*; a recent study conducted on mice in fact suggests that Parkinson's disease begins in the gut and not in the brain.[12] Affected patients begin to experience constipation at least a decade before other, more obvious symptoms show up leading to the new understanding that gut bacteria play an important role in regulating Parkinson's Disease.
12. *Soft or low voice* even when speaking in normal tone
13. *Masked face*; serious, depressed looking face even when patient may not feel so
14. *Dizziness or fainting*
15. *Stooping or hunching over*; inability to stand straight, tendency to lean or slouch when standing.

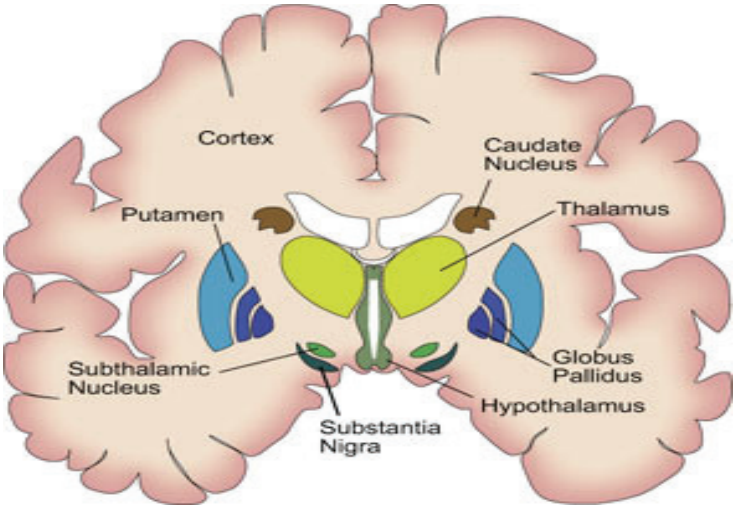

Figure 1. The basal ganglia[7]

Formation, Function and Relevance of Lewy Bodies in Parkinson's disease

Lewy Bodies were named after Dr Friederich Lewy, a German neurologist who discovered them as a cause of disruption in brain's normal functioning.[13] They are abnormal deposits of a protein called alpha-synuclein in the brain which actually plays a number of important roles, especially at synapses. They alter the normal functioning of the brain by affecting certain chemicals which can in turn result in problems thinking, movement, behaviour and mood. They are always found in the substantia nigra and other specific brain regions in Parkinson's Diseases patients.[13, 14]

Due to this, Lewy Bodies serve as a diagnostic marker and have also proved to be essential for the pathological diagnosis of specified cell loss (in the brain, for Parkinson's disease). Their distribution is fairly specific and only consists of medium to large sized monoaminergic and cholinergic neurons of the substantia nigra, nucleus basalis of Meynert and hypothalamus and sometimes in parts of the cerebral cortex, thalamus and autonomic ganglia, affecting the autonomic nervous system.[14]

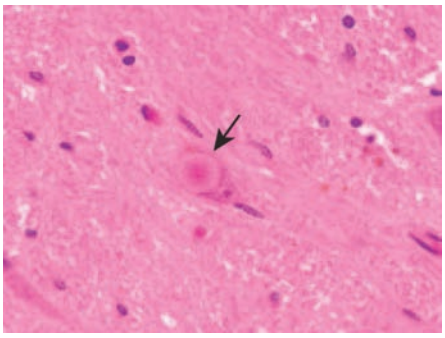

Figure 2. Lewy body in substantia nigra.

In addition, the apparent absence of retrograde degeneration also serves as one of the main characteristics of the disease progression. Almost always, the cells in which


they are isolated are dead.[14] Due to these facts; Lewy Bodies are considered important markers of neuronal degradation.[3]

These abnormal protein aggregates are usually eosinophilic, intracytoplasmic, round and come with a diameter of 5-25μm. While most of them consist of a central body surrounded by a pale-staining halo (as seen in figure 2), there can be other, less common forms either with a darker core or rings. In addition, they can also be found in nerve cell processes and neuropil of dying cell. It is the great packing density and apparent structural degradation of filaments that account for its eosinophilic and halo appearance.[14]

In a study conducted to clarify the size and characteristics of the population with incidental Lewy Body disease, it was found that there were destruction and loss of nigral cells of a severity ranging from intermediate to normal. It was also found that surrounding nuclei such as those in locus coeruleus and nucleus basalis of Meynert could also be involved.It also proved that people in their fifties to eighties are the ones with the greatest percentage of Lewy Bodies in their brains.[14] Other than playing a major in the diagnosis and determination of the severity of Parkinson's disease, Lewy Bodies are also found in patients suffering from Lewy Body Dementia (LBD).[13]

Dementia involves a severe loss of thinking abilities which then interfere with a person's capacity to carry out their daily activities. It may be due to a variety of causes such as stroke, brain tumor, depression and vitamin deficiency. They may also occur due to *disorders* such as LBD, Parkinson's and Alzheimer's disease.[13] They need to be diagnosed carefully keeping in mind that dementia may either occur alone or along with either of Alzheimer's or Parkinson's disease. Its progressive development also makes diagnosis harder and on average, it may last anytime from five to seven years and may elapse from the time of diagnosis to subsequent death of the patient.[13]

Most dementia Lewy bodies cases coming to autopsy are of men. When viewing samples under the microscope for the presence of Lewy bodies, they may be seen as round, eosinophilic bodies with a visibly darker core and pale surrounding rings. Parkinson's disease is a neurodegenerative condition occurring in the substantia nigra of the basal ganglia which in turn has complex anatomy and physiology which need to be understood in order to understand the development of the disease.

A study aimed at identifying the size and characteristics of the population with incident Lewy bodies confirmed Parkinson's disease involves destruction and loss of nigral cells due to the presence of Lewy bodies. Several studies, both completed and ongoing suggest that stem cells pose great potential in tackling the disease. This can date back to the late 1970s and early 1980s when it was found that dopaminergic neurons harvested from developing fetal midbrain had the potential to survive grafting in animal models when transplanted in adult striatum where the released dopamine and made connections from host brain to itself. [15]

CONCLUSION

Lewy bodies, which are abnormal aggregates of alpha-synuclein, are very important biomarkers in Parkinson's disease. However, the disease itself cannot be diagnosed early due to its progressive nature and range of symptoms that overlap with other common neurodegenerative diseases such as Lewy body dementia and Alzheimer's disease. Current work focuses on producing dopaminergic neurons from stem cells under appropriate conditions.

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