International Advance Journal of Engineering, Science and Management (IAJESM)
ISSN -2393-8048, July-December 2021, Submitted in October 2021, iajesm2014@gmail.com

Study on Neuropathological Features of Parkinson's Disease

Sayyad Sajauddin Gulab Research Scholar, Department of Pharmacy, Sunrise University, Alwar, Rajasthan (India)
Dr. Dhirendra Babji Sanghai, Professor, Department of Pharmacy, Sunrise University, Alwar, Rajasthan (India)
Email: sdsnforu@gmail.com

Abstract

PD is characterized by two hallmark pathological features which even today help in diagnosing the disease. The first feature is the progressive loss of dopaminergic (DA) neurons in the *substantia nigra* pars compacta (SNpc) of the ventral midbrain. DA neurons of the SNpc innervate the putamen and caudate via the nigrostriatal pathway and thereby exert a stimulating function to the striatum which regulates motor control. Lossof DA neurons leads to subsequent degeneration of the entire nigrostriatal pathway. The second feature is the presence of intra-neuronal inclusions known as Lewy bodies. These are spherical, eosinophilic cytoplasmic protein aggregates composed of numerous proteins including α-synuclein, parkin, ubiquitin, and neurofilaments, and they are found in all affected brain regions. At the onset of symptoms, putamenal DA is depleted by around 80% and of SNpc by 60%. Also, neuromelanin, an extraneuronal pigment is observed abundantly resulting from the neuronal loss.

Keywords: PD, Neurological, disease

Introduction: Another feature not much written about but significantly demonstrated in a majority of patients is gliosis due to extensive brain damage. It remains unclear why dopaminergic neuronal cell death and Lewy body formation occur in PD[1].

The pathological changes in PD follow a specific sequence initially affecting the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus. Itthen proceeds to the coeruleus-subcoeruleus complex, pedunculo-pontine nucleus, reticular formation of the raphe nucleus and then ultimately to parasympathetic as well as sympathetic post-ganglionic neurons and the cerebral cortex. Widespread neuropathologyin the brainstem and cortical regions are responsible for various motor as well as the non-motor symptoms of PD[2].

Clinical features:

The symptoms of PD begin insidiously and gradually worsen with age. Clinical presentation may vary from patient to patient, and it is not uncommon for PD symptoms to go unrecognized or unreported for years. Four cardinal motor manifestations are the central features of PD: resting tremor, bradykinesia (slowness of movement), rigidity often with a cogwheel quality and postural instability[3]. Initially, fatigue is associated withcommonplace actions such as getting up, initiating movements and carrying out movements at similar speeds as before. However, the most obvious symptom recognized early in the disease is the asymmetric **rest tremor** (70-90% of patients)[4]. It is more common in younger patients but is rarely a major cause of disability. Initial symptoms usually begin on one side of the body and continue to remain so for some time. **Bradykinesia** is the most disabling feature of the disease, more prominent in elderly patients and contributes to difficulties in arising from a chair or getting in or out of the car. The extreme of bradykinesia is akinesia, or the inability to initiate movement. Bradykinesia, particularly when combined with rigidity, may manifest as micrographia if the dominant hand is involved. Bradykinesia also is manifested as very slow movement, hypophonia (weak voice or whispering as a result of un-coordination of muscles of vocalization), reduced dexterity, a masked face, drooling and a slow, shuffling gait. **Rigidity** involves tightness or increase in muscle tone at rest or throughout the entire range of motion of a limb. **Postural instability** which involves loss of balance giving a feeling of unsteadiness is a sign of more advanced PD[3].

The early symptoms and signs of PD—rest tremor, bradykinesia, and rigidity—are related to progressive loss of nigrostriatal dopamine. These signs and symptoms result from striatal dopamine deficiency and are usually treated by levodopa and dopamine agonists. As PD

progresses over time, symptoms that do not respond to levodopa develop, such as flexed posture, the freezing phenomenon, and loss of postural reflexes; these are often referred to as non-dopamine- related features of PD. Moreover, bradykinesia that responded to levodopa in the early stage of PD increases as the disease worsens and no longer fully responds to levodopa[5]. Besides the motor symptoms which dominate the clinical picture of PD, many patients also develop a number of non-motor symptoms which tend to be even more disabling. These significantly affect the health-
related quality of life of both the patients and the caregivers. Depression is frequent in PD, affecting up to 50% of patients. Depression is often associated with anxiety and can occur at any stage of the illness, including prior to onset of motor symptoms. Other non- motor features that may occur early in PD are cognitive impairment and olfactory dysfunction (reduced ability to smell odours or even complete loss of smell)[6]. Cognitive impairment in PD is characterized by difficulties in executing tasks, memory retrieval deficits, and impairment in attention, with advancing age being the primary risk factor[6] [7]. Psychosis, specifically hallucinations and delusional thinking, is also common in PD, seen in 15% to 40% of treated patients and tending to occur later in the disease course[8]. Other symptoms include autonomic dysfunction such as dysphagia, impaired gastrointestinal motility, bladder disturbances such as nocturia, orthostatic hypotension and sleep disorders like insomnia, daytime somnolence, rapid eye movement disorder etc[3].

Etiology:

From the time PD has been defined and described, its understanding has increased over the years with improvements in scientific techniques and a surge in neurodegenerative research. There was one repeated observation in studies being carried out that PD was clearly being inherited in a Mendelian fashion in large families[9]. This point opened up an entire new angle to study the disease since it had been termed idiopathic all this time. Thus, twenty years of researching the genetic aspects of PD have led to the identification of several monogenic forms of PD and certain genetic factors increasing the risk of developing PD. Monogenic forms, caused by single mutation, duplication or triplicationin a dominantly or recessively inherited gene have introduced a new category of PD known as familial PD. These monogenic forms account for approximately 30% of familial and 3-5% of sporadic cases[10]. The first mutations responsible for PD were mapped and identified in 1996 firmly establishing the hereditable nature of PD. Till date, 28 distinct chromosomal regions known as loci and 11 genes have been more or less associated with PD as either a cause or a risk factor through a combination of genetic linkage analysis and genome wide association studies[10] [11]. The chromosomal loci termed as PARK and some of the associated genes discovered were PARK1 and PARK4/*alpha* synuclein (*SNCA*), PARK2/*parkin*, PARK5/*ubiquitin COOH-terminal hydrolase L1*
(*UCHL-1*), PARK6/*phosphatase and tensin homolog induced putative kinase 1* (*PINK-1*), PARK7/*DJ-1*, PARK8/*leucine rich repeat kinase 2* (*LRRK2*), PARK9/*ATPase type 13A2* (*ATP*13A2), PARK11/*growth factor receptor bound protein 10-interacting GYP protein*
2 (*GIGYF2*), PARK13/*Omi/Htra2* (*HTRA2*), PARK14/*phospholipase A2 group VI* (*PLA2G6*), and PARK15/*F-box protein 7* (*FBXO7*)[11]. Among these, *SNCA, LRRK2* and *VPS35* (recently associated with PD) were associated with autosomal dominant form of PD whereas the rest of the genes were accountable for the autosomal recessive form of PD. Among all these genes, till date, mutations only in *SNCA* and *LRRK2* have been found to mimic sporadic disease at both clinical and pathological levels[12]. LRRK2 is a huge protein, appearing to play a central role in the pathophysiology of PD and is associated with alpha synuclein pathology and other proteins implicated in PD[13]. The focus of the research being understanding the combined role of SNCA and LRRK2 in PD, emphasis has been given to studying these two proteins.

Role of Alpha synuclein in pathophysiology of PD:

Discovery:

Alpha synuclein was identified using an antibody against cholinergic vesicles giving hints as to its presynaptic role. It was found to be localized at the nucleus since the antibody also detected its expression at the nuclear envelope thus its landing the name "synuclein"[14]. It was discovered as a precursor for the non-amyloid beta-component (NAC) of amyloid plaques characteristic of Alzheimer's disease[15]. It was also identified as an inhibitor of phospholipase D (PLD2), giving it a specific biochemical role. PLD enzymes had been initially implicated in membrane trafficking especially in exocytosis. The quest to identify regulators of PLD2 lead to the discovery of α-synuclein and its closely related isoforms β and Ɣ synucleins[14 16].

Structure:

Synucleins belong to a family of 15 to 25 kDa proteins and although they share considerable sequence homology, alpha synuclein has a unique amyloidogenic region in its middle known as the NAC domain which is capable of aggregating and forming intermediate oligomeric structures called protofibrils and ultimately insoluble polymeric fibrils[17]. Structurally, it is a small 140 amino acids protein, with 7 imperfect repeats (KTKEGV) in the N-terminal domain, the middle NAC domain and the C-terminal
negatively charged acidic domain. It exists in both free cytosolic and membrane bound form, as much as 15% is membrane bound in neurons[18 19]. Although natively unfolded with no secondary structure (just a random coil), alpha synuclein adopts an alpha helically rich structure, once it binds to phospholipid membranes mostly through its amino terminal repeats, inspite of its not having a well-defined membrane binding domain[17 20 21]. The amino terminal domain contains apolipoprotein lipid binding motifs which are hypothesized to form amphiphilic helices which assist in forming the alpha helices on binding to membranes[22].

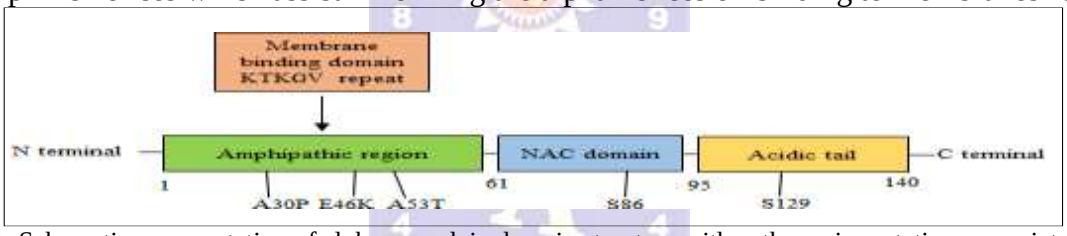

Fig 2.1: Schematic representation of alpha synuclein domain structure with pathogenic mutations associated with PD and certain phosphorylation sites.

Membrane interactions and localization:

SNCA interacts weakly with cell membranes but shows a preference for membranes with high curvature which is why it interacts with synaptic vesicles. Also, this might be the reason why it dissociates from vesicles during exocytosis due to its coming in contact with the relatively flat plasma membrane. The reason behind the preference of SNCA for structures with high curvatures lies in its structure. The hydrophobic face of the N terminal domain of α-helix contains a series of threonine residues at position 3 in the repeat and also its precise positioning in repeats 2-5 and 7 is conserved across all synucleins. Threonine at all these positions weakens the interaction of synucleins with membranes so that it's interaction with structures with high curvatures is increased. An experiment was conducted to test this hypothesis by replacing threonine in synuclein with large non-polar residues such as leucine and phenylalanine and the interaction of synuclein with membranes was observed. It was found that the protein lost specificity forboth membranes and vesicles[23].

References:

1. Kanazawa I. How do neurons die in neurodegenerative diseases? *Trends Mol Med*. 2001. doi:10.1016/S1471-4914(01)02017-2

2. Olanow CW, Tatton WG. Etiology and pathogenesis of parkinson's disease. *Annu Rev Neurosci*. 1999;22(1):123-144. doi: 10.1146/annurev.neuro.22.1.123

3. Chen S-Y, Tsai S-T. The Epidemiology of Parkinson's Disease. *Tzu Chi Med J*. 2010;22(2):73-81. doi:10.1016/S1016-3190(10)60044-4

4. Weintraub D, Comella CL, Horn S. Parkinson's disease--Part 1: Pathophysiology, symptoms, burden, diagnosis, and assessment. *Am J Manag Care*. 2008;14(2 Suppl): S40-8. http://www.ncbi.nlm.nih.gov/pubmed/18402507.
5. Stacy M, Jankovic J. Current Approaches in the Treatment of Parkinson's Disease. *Annu Rev Med*. 1993;44(1):431-440. doi:10.1146/annurev.me.44.020193.002243
6. Goetz CG. The History of Parkinson's Disease: Early Clinical Descriptions and Neurological Therapies. *Cold Spring Harb Perspect Med*. 2011;1(1): a008862- a008862. doi:10.1101/cshperspect. a008862