

Alzheimer and Parkinson's Disease -Two Faces of the Same Disease?

Atanu Biswas and Shyamal Kumar Das*

Cognitive Disorders and Movement Disorders Clinics, Department of Neurology, Bangur Institute of Neurosciences (BIN) and Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata, India

The growing elderly population is increasing the number of persons with late-onset diseases such as Parkinson's disease (PD) and Alzheimer disease (AD) throughout the world. These two diseases are not related but they do have some similarities. Both are neurodegenerative diseases and typically begin late in life. Both are characterized clinically by slow and progressive disease course and pathologically by neuronal degeneration with intra neuronal inclusions. Although initial symptoms differ, both diseases lead to dementia.

Apart from these apparent similarities, two diseases are completely different. PD is primarily a movement disorder that can eventually develop cognitive impairment and dementia characterized by visuospatial impairment and fluctuations in mental state. However, many individuals with PD never develop cognitive impairment during the course of their illness. On the contrary, AD is primarily a dementing illness which begins with episodic memory impairment and subsequently progresses to impairment of other cognitive domains. Very late in the course, AD patients develop parkinsonian features.

Dementia in advanced PD is difficult to differentiate from AD and both can coexist in the same person. It is sometime difficult to distinguish the two based on clinical evaluation, imaging and with biomarkers.

Lewy body is the pathological hallmarks of PD. Lewy bodies are intra neuronal inclusions resulting from aggregation of alpha-synuclein which lead to neuronal cell death through various biochemical processes. The core motor symptom of PD results from degeneration of dopaminergic neurons in substantia nigra. The disease however, has numerous non-motor features arising from degeneration of serotonergic, cholinergic, and catecholaminergic neurons in different parts of brain. Clinico-pathological associations of dementia in patients with PD are classified into three groups on the basis of pathological changes like, subcortical pathology with Lewy-bodies, limbic or cortical Lewy-body-type degeneration, and coincident AD-type pathology [1].

AD, on the other hand is characterized by deposition of extracellular amyloid plaques and intraneuronal neurofibrillary tangles (NFT) which is composed of hyper phosphorylated *tau* protein, the main cytoskeleton protein responsible for microtubule formation within neurons. The AD pathology first begins in the hippocampus and the entorhinal cortex, the areas critical for learning and memory. It then spreads to other parts of the cerebral cortex. Loss of cholinergic innervations of the cortex is an important pathophysiological process for AD. The worsening of memory and general intellect progress and may become severe without any motor impairment till late in the disease.

Various studies have shown that AD patients carry the Lewy body pathology (LBP), higher than by chance suggesting pathological heterogeneity of AD [2]. There is pathological evidence of Lewy body deposition in AD and it is more extensive in familial AD cases particularly with presenilin-1 mutation and in AD cases with variant pathology [2,3]. In these familial AD cases, the first LBP appears in the amygdala, in contrast to PD where the first LBP may occur in the medulla. It has also been found that AD and LBP have a different clinical phenotype with more neuropsychiatric as well as parkinsonian motor features as evidenced by neuropsychiatric inventory (NPI) and

United Parkinson Disease Rating scale (UPDRS) motor scores which may help to distinguish them from AD alone [4]. Conversely, amyloid plaques and tangle deposition has been reported in some patients with PD as compared to age-matched control with there being a correlation between a cortical amyloid pathology, a neurofibrillary tangle pathology, and dementia in PD [5].

A *tau* neuropathology is considered to be a hallmark of AD, and also in some parkinson-plus syndromes like progressive supranuclear palsy (PSP) and on a genetic level, variants in *MAPT* (the microtubule-associated protein Tau), are the strongest risk factor for PSP. However, using only neuro pathologically proven PD cases, Charlesworth G, et al. [6] showed a strong association with the *MAPT* gene with idiopathic PD and it was independent of the PSP association.

As two diseases are commonly associated with aging and both can coexist, a common genetic linkage is investigated in various studies. Studies that have investigated the extent to which these two diseases co-occur in families have produced varying results. While some have reported either no increased risk of AD in the relatives of patients with PD, others have shown an increased risk of AD in younger patients with PD or those with cognitive impairment [7-9]. It may be possible that the misdiagnosis of dementia with Lewy bodies (DLB) or PD dementia may have confounded some of these older studies that reported a clinical overlap between AD and PD.

To examine this, a large genome wide association (GWA) study involving more than 3000 AD and more than 5000 PD cases was conducted and researchers found no common genetic variants that increase the risk of developing both diseases [10]. Therefore, it may be said that people who are genetically predisposed to developing PD do not automatically have an increased genetic risk for AD.

In another GWA study of a neurologically proven large cohort of DLB, investigator found APO E was a strong genetic risk factor for the disease [11]. They also argued that lysosome played an important role in the etiology of the DLB.

In another study looking at genetic correlation between DLB, PD, and AD; researchers showed that DLB shared approximately the same amount of genetic determinants with PD as it did with AD, when the APOE locus was excluded [12].

Being neurodegenerative diseases, abnormal proteins are found

*Corresponding author: Shyamal Kumar Das, Professor and Head, Department of Neurology, Bangur Institute of Neurosciences, 52/1A, S.N. Pandit Street, Kolkata-700 025, India, Tel: +91 33 2223 7722; E-mail: das_sk70@hotmail.com

Received February 22, 2016; Accepted March 10, 2016; Published March 17, 2016

Citation: Biswas A, Das SK (2016) Alzheimer and Parkinson's Disease -Two Faces of the Same Disease? J Alzheimer's Dis Parkinsonism 6: 222. doi: [10.4172/2161-0460.1000222](https://doi.org/10.4172/2161-0460.1000222)

Copyright: © 2016 Biswas A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

aggregating in the brain in both the diseases; *tau* and amyloid in AD and alpha-synuclein in PD. Studies have shown some overlap in the pathology of AD and PD: more than 50 percent of people with AD show alpha-synuclein deposits and people with PD commonly have *tau* deposits. In experimental study involving mice and neuron cell cultures, researchers have found specific strains of alpha-synuclein help the accumulation of the *tau* protein in brain cells [13]. They speculated that distinct strains of pathological alpha-synuclein likely exist in neurodegenerative disease brains and may underlie the tremendous heterogeneity of synucleinopathies. This might explain how people with PD develop AD like pathology in the brain.

As in most of the adult-onset neurodegenerative diseases, AD and PD are associated with protein mis folding and possibly prion-like spreading within the nervous system. The mis folding makes these proteins vulnerable for aggregation. The endoplasmic reticulum is thought to be the site for synthesizing defective protein and lysosome for faulty disposal of these mis folded proteins. The neuropathology-based classification emphasizes that protein deposits show a hierarchical involvement of brain regions and a possible prion-like spreading is thought to take place for the propagation of pathology within the nervous system.

Due to the frequent coexistence of synucleinopathy and tauopathy targeting the protein processing systems may help to maintain the healthy homeostasis of cells and to protect the physiological forms of neuro degeneration-associated proteins [14]. Future treatment strategies would be through modifications of these proteins and preventing them from getting misfolded [15].

References

1. Emre M (2003) Dementia associated with Parkinson's disease. *Lancet Neurol* 2: 229-237.
2. Leverenz JB, Fishel MA, Peskind ER, Montine TJ, Nochlin D, et al. (2006) Lewy Body Pathology in Familial Alzheimer Disease: Evidence for Disease- and Mutation-Specific Pathologic Phenotype *Arch Neurol* 63: 370-376.
3. Lippa CF, Pulaski-Salo D, Dickson DW, Smith TW (1997) Alzheimers disease, Lewy body disease and aging: a comparative study of the perforant pathway. *J Neurol Sci* 147: 161-166.
4. Chung EJ, Babulal GM, Monsell SE, Cairns NJ, Roe CM, et al. (2015) Clinical features of Alzheimer disease with and without Lewy bodies. *JAMA Neurol* 72: 789-796.
5. Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, et al. (2011) Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain* 134: 1493-1505.
6. Charlesworth G, Gandhi S, Bras JM, Barker RA, Burn DJ, et al. (2011) Tau acts as an independent genetic risk factor in pathologically proven PD. *Neurobiol Aging* 33: 838.e7-838.11.
7. Marder K, Tang MX, Alfaró B, Mejia H, Cote L, et al. (1999) Risk of Alzheimer's disease in relatives of Parkinson's disease patients with and without dementia. *Neurology* 52: 719-724.
8. Levy G, Louis ED, Mejia-Santana H, Cote L, Andrews H, et al. (2004) Lack of familial aggregation of Parkinson disease and Alzheimer disease. *Arch Neurol* 61: 1033-1039.
9. Rocca WA, Bower JH, Ahlskog JE, Elbaz A, Grossardt BR, et al. (2007) Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. *Arch Neurol* 64: 1458-1464.
10. Moskvina V, Harold D, Russo G, Vedernikov A, Sharma M, et al. (2013) Analysis of genome-wide association studies of Alzheimer disease and of Parkinson disease to determine if these 2 diseases share a common genetic risk. *JAMA Neurol* 70: 1268-1276.
11. Bras J, Guerreiro R, Darwent L, Parkkinen L, Ansorge O, et al. (2014) Genetic analysis implicates APOE SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. *Hum Mol Genet* 23: 6139-6146.
12. Guerreiro R, Escott-Price V, Darwent L, Parkkinen L, Ansorge O, et al. (2016) Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases. *Neurobiol Aging* 38: 214.e7-e214.e10.
13. Guo JL, Covell DJ, Daniels JP, Iba M, Stieber A, et al. (2013) Distinct alpha-synuclein strains differentially promote tau inclusions in neurons. *Cell* 154: 103-117.
14. Kovacs GG (2016) Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine. *Int J Mol Sci* 17: 189.
15. Hamilton RL (2000) Lewy bodies in Alzheimer's disease: a neuro pathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol* 10: 378-384.