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Review Article

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Similarities among Alzheimer's Disease, Parkinson's Disease and Dementia may Call for a Similar Treatment

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Abstract

Alzheimer's Disease (AD), Parkinson's Disease (PD), and Dementia are all age-related neurodegenerative diseases. In the US, AD victims are increasing every year from 5.5 million in 2018 to 13.8 million by 2050. PD patient are calculated to increase from 7K to 1 million by 2030. Results from accumulation of extracellular amyloid-β (Aβ) peptide and deposition of intracellular *tau* aggregated tangles. The prognosis of AD and PD both is the onset of Dementia, which causes memory impairment irreversibly, thinking capabilities, orientation, comprehension, learning any new things, and taking the judgment. Dementia is currently the seventh leading cause of death among all diseases worldwide. Here we will discuss the similarities in the disease nature and cause of AD, PD and Dementia at their cellular and molecular level to find a common therapy for them (Graphical Abstract).

Keywords

Alzheimer's disease (AD), Parkinson's Disease (PD), Dementia, Tangles, Plaques, Cognitive function

Abbreviations

AD: Alzheimer's Disease; LOAD: Late-Onset AD, SPs: Senile Plaques; NMDA: N-methyl-D-aspartate; Aβ: Amyloid-Beta Peptide; EphB2 receptors: Ephrin type-B receptor 2; NFTs: Neurofibrillary Tangles; ApoE: Apolipoprotein E; p*Tau*: Hyperphosphorylated *tau*; BACE1: β-site APP Cleaving Enzyme type-I; APP: Amyloid Precursor Protein; LTD: Long-term Depression; EOAD: Early-Onset AD; MTs: Microtubules; PSEN1 and PSEN2: Presenilins 1 and 2; p*tau*: Phosphorylated '*tau*'; AICD: APP Intracellular Domain; Cdk-5: Cyclin-Dependent Kinase 5; sAPPβ: Soluble Ectodomain-β; cdc-2: Cell-Cycle Kinase; sAPPα: soluble Ectodomain-α; ROS: Reactive Oxygen Species

Introduction

The typical neurodegenerative diseases are Parkinson's disease (PD) and Alzheimer's disease (AD) and Dementia [1]. Both PD and AD display mitochondrial dysfunction and oxidative stress [2-4], while Dementia is a broad term that stands for an irreversible loss of thinking ability, memory, and other mental capabilities [5,6]. In fact, Dementiais considered as the end results of AD and PD. All these diseases are believed to be due to aging. This article will discuss the similarities and differences among these neural diseases and find for some appropriate treatment possibilities [7-75] (Table 1, Table 2, Table 3, Table 4, Table 5, Table 6 and Table 7).

Conclusions

The greatest risk factor for AD, PD and Dementia is age. It appears thattau and Aβ are the hallmarks for both AD and PD in the brain and eventually for Dementia [76,77].

This review indicates large similarities in genetic risk factors between diseases, AD, PD and Dementia. The genes that were discussed above have the possibility as a potential biomarkers.

Using KEGG pathway analysis [78], Wang, et al. discovered that PD and AD were both dysfunctional in synaptic vesicle and mitochondrial oxidative metabolism pathways [79]. The enriched genes in AD cases was greater than PD. Although PD and AD have common characteristics [80]; cognition and patients with learning or memory damage in AD was more severe than in PD [81].

Epigenetic regulatory mechanisms, such as chromatin remodeling, DNA methylation, histone variant and histone post-translational modification have been suggested to regulate numerous aspects of axonal development and neuronal survival [82]. One study presented evidence that

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Table 1: Basic information of the diseases.

	AD	PD	Dementia
Affected Region/ Cause:	• Extensive neuronal loss that leads to brain tissue atrophy. • Neurofibrillary tangles in the neocortex and hippocampus [7]. • Extracellular amyloid- (Aβ) deposits, senile plaques and amyloid plaques [8].	• Neuron degeneration and loss of dopamine in the substantia nigra pars compacta in the midbrain [9,10].	• Like AD and PD, Dementia is also an aging issue, but loss of neural cells due to some neurotoxic agents, external brain injury is also prevalent.
Symptoms:	• Progressive memory loss. • Affects cognitive functions such as communication and movement [11].	• The clinical manifestations of PD are bradykinesia, resting tremor and postural instability [11].	• Getting lost • Trouble with complex but familiar tasks, like fixing a meal or paying bills • Personality changes, like depression, agitation, paranoia, and mood swing
Age of Onset:	Late-onset variety-symptoms first appear in mid-60s. Early-onset AD begin between a peson's 30s and mid-60s [12].	• The average age of Parkinson's disease is 56. • Around 4 percent of Parkinson's patients are diagnosed before the age of 50. • The youngest recorded case of Parkinson's was a 12-year-old patient [13].	• Dementia is commonly found in people over the age of 65. However, it can affect people in their 30s, 40s, or 50s [14].
Prognosis:	• Prognosis Dementia (Irreversible loss memory)[12]	• Prognosis Dementia (Irreversible loss memory)[13]	• Dementia is a severe disease with a poor prognosis. Mortality risks are estimated to be at least two times higher than mortality risks in non-demented patients [15] • It is expected that Dementia will be among the leading causes of death in the near future instead of cardiovascular diseases (CVDs) [16,17]

Table 2: Molecular basis of the diseases.

<table>
<tr><th>AD</th><th>PD</th><th>Dementia</th></tr>
<tr><td>• Mutations of the β-amyloid (Aβ) precursor protein on chromosome 21, cause Alzheimer disease (AD) [18].
• Lewy bodies are a marker protein aggregation in PD, are also frequently observed in cases of classic AD, including in patients with mutations in APP, PSEN1, and PSEN2 [19,20].</td><td>• The main neuropathologic hallmark of PD is the accumulation of α-synuclein in neurons in the form of Lewy bodies [21].</td><td>• Lewy Body Dementia (LBD) is a common type of degenerative Dementia in elderly people [22].
• Many patients with LBD have AD pathology because they have Lewy bodies, cortical amyloid plaques and neurofibrillary tangles in common [22].</td></tr>
<tr><td colspan="3">In transgenic mice, the accumulation of α-synuclein could significantly disrupt cognition [20].</td></tr>
<tr><td colspan="3">It is generally believed that oxidative stress and mitochondrial dysfunction are likely to be the common mechanisms in PD, AD and Dementia [23].</td></tr>
<tr><td colspan="3">• Linkage analysis showed that the better part of AD signal on chromosome 12q13 near 50 Mb was actually caused by a subset of families fulfilling neuropathological criteria for LBD (i.e., 8 of 54 families) [24-26].</td></tr>
<tr><td>• Mutations in microtubule-associated protein tau.</td><td colspan="2">• Abundance of 4-repeat tau has also been frequently associated with PD. This possibly suggests a common tau-related pathogenic mechanism shared by FTD and late-onset PD [27].</td></tr>
<tr><td>• Fully penetrant autosomal dominant mutations in 3 genes (i.e. APP, PSEN1, and PSEN2) has been shown to cause AD [28-30].</td><td>• Mutations in at least 5 genes has been shown to cause familial early-onset Parkinsonisms:
--(α-synuclein [SNCA or PARK1] [31];
--parkin [PRKN or PARK2] [32]
--DJ-1 [DJ1 or PARK7] [33]
--PTEN-induced putative kinase I [PINK1 or PARK6] [34];
--leucine-rich repeat kinase2 [LRRK2 or PARK8] [35,36].</td><td>• Rare missense mutations
In MAPT leads to a syndrome of fronto-temporal dementia (FTD) with parkinsonism linked to chromosome 17 [FTDP-17] [24].</td></tr>
</table>

Table 3: Cellular basis of the diseases.

AD	PD	Dementia
• Both sirtuin and REST signaling pathways are disturbed both the diseases, AD, PD [37].		• Affected neurons display intracellular *tau*-positive inclusions that are distinct from the neurofibrillary tangles observed in AD [39].
• Lewy bodies, protein aggregation and α-synuclein in PD are also found in > 60% of AD cases [38].		• The first FTD mutations were identified in cases accompanied by Parkinsonism and showing genetic linkage to chromosome 17q21, near the *tau* gene (FTDP-17) [24]
• AD cases have *tau* tangles.	• *tau* aggregation is shown in ~50% of PD cases snRNP70 may co-localize in PD cases [40].	• Subsequently, disease-causing mutations were identified in *tau* (gene: MAPT) [22].

Table 4: Genes involved.

AD	PD	Dementia
• The strong risk factor for AD, ApoE4, has been related to cognitive decline in PD [42] and Dementia also [43-45].		
• Genetic overlap between AD, PD and Dementia was also discovered [46,47].		
• Genetic association study proved rs76904798 of LRRK2 significantly reduce late-onset AD risk in Han Chinese [47]; and it is found Dominant in dementia [35,36].		
• APP: Ab precursor protein, Dominant [48].	• PRKN: Parkin: Recessive [32]	
• PSEN1: Presenilin1; Dominant [28]	Recent reports have suggested that some cases of PD and FTD may also be caused by mutations in PSEN1 [49]	
• PSEN2: Presenilin 2: Dominant [29,30].	• PINK1: PTEN induced putative kinase 1: Recessive [34].	
• The rs356182 locates in the intron of SNCA, which is the coding gene of α-synuclein which has key role PD genesis [50-52].	• SNCA: α-synuclein: Dominant [31].	
MAPT: Microtubule-associated protein *tau*: Dominant [22].	DJ1: DJ1: Recessive [33].	
The AD risk factor SORL1 had been identified to be associated with PD recently [53].		

Table 5: Epigenetics of the diseases.

AD	PD	Dementia
• Single nucleotide polymorphism (SNP) analysis of PD and AD revealed that 12 of them, such as EPB41L5, CYP26B1, IQCB1, DCP1A, CLGN, TDRD6, PSORS1C1, PARP12, WISP1, PIK3C2A, CLMN, DHX33, are common in them [37].		
• SNRNP70 encodes the small nuclear ribonucleoprotein snRNP70 co-localizes with *tau* in AD [54].	The hub gene SNRNP70 has been shown to be differentially expressed in PD blood and Dementia [55].	

Table 6: Possibilities of gene therapy.

AD	PD	Dementia
Gene therapy can be used to treat diseases by the introduction of therapeutic genes, by replacing, silencing, or correcting faulty genes.		
• APOE is the genetic risk factor. Significantly increases the incidence of late-onset AD (LOAD) [56,57]. • ECE can participate in Aβ degradation and could be a potential target for a pharmacological or gene therapeutic approach [58,59]. • Lentivirus mediated gene delivery of cathepsin B reduced anti-Aβ antibody, and Thioflavin S-positive amyloid plaques, supporting a role for cathepsin B in Aβ degradation [64]. • Gene delivery of IDE could possibly enhance Aβ degradation and influence AD pathology [66,67]. • Down-regulation of AD-associated proteins, BAC1, APP, by siRNA [66,67].	• Genome editing of mutations in several genes associated with both familial- and sporadic PD, including parkin, LRRK2, SNCA, PINK1, DJ-1, VPS35, DNAJC13, CHCHD2 [59]. • Gene therapy with growth factors and also some non-disease modifying targets, such as TH, GCH and AADC and VMAT2 could be relevant treatment for patients [60].	• Approximately 30% of patients with FTD show a clear autosomal dominant inheritance pattern, where one copy of a mutated gene causes the genetic condition. • The three genes commonly involved in hereditary of FTD are **granulin (GRN)**, C9orf72 and MAPT [61,62]. • AAV gene therapy is a potential avenue for disease modification in GRN carriers [68,69].

Table 7: Possibilities of cell therapy.

AD	PD	Dementia
Cure may be possible if right cell can be transplanted which can grow, produce dopamine, can survive for longer period of times, but can differentiate, and should not have any ethical issues.		
• **Neural stem cells (hNSCs):** Stem cells have high migratory capacity after transplantation into the brain, and can be genetically modified in vitro. Therefore, they can be an efficient candidate to deliver neurotropic factors or enhance gene expression to modify the course of the disease [70-72]. • They also release DA in response to substrate (DOPA)-induced condition than those obtained in control groups [73]. • These cells also express DAT (Dopamine Transporter), that controls the physiological label of DA in the synaptic cleft [73].		
ESCs-derived NPCs: Transplantation of these cells into the injured hippocampus demonstrate the formation of synapses between host and grafted neural cells, and also improve the memory dysfunction [74,75].		
Induced pluripotent stem cells (iPSCs): Neurons derived from human iPSCs are endowed with a remarkable potential to establish orthotropic long-range projections in the adult mammalian brain [76].		
NSCs: In mouse AD model, the transplantation of NSCs was reported to improved cognition function mediated by the neurotropic factor BDNF [77].		

changes in H3K27ac or H3K4me3 occurred in connection with genetic variants in AD. This is an important function for immune-associated enhancers and promoter proteins in determining AD susceptibility [83]. Another study demonstrated that H4K16ac, a histone associated with DNA repair and neurodegenerative disorders, is significantly reduced in the cortex of AD patients. This suggests that the aged brains of these individuals are incapable of up-regulating H4K16ac [84]. In addition, multiple reports have associated loss of H3K4me3, a protein related to gene activation, with the deterioration found in PD. Overexpression of H3K4me3 can accelerate A-T mutation that mitigates behavioral impairments and neurodegeneration [85-87].

HDAC inhibitors can prevent neuro-degeneration in models of AD [88-91]. This paper demonstrate that epigenetic profiles are regulated in neurodegenerative diseases and gives a better understanding of these mechanisms that can provide the foundation for developing more precisely targeted epigenome therapies. For example, recent work suggesting that epigenetic editing can improve cognition in AD highlights the potential of epigenetic regulation-based gene therapy for neurodegenerative disorders [92].

Gene modification of stem cells prior to transplantation can be useful for increasing cell survival and making them more effective [93]. Due to the loss of cholinergic neurotransmitters in AD, gene-modified cells transplantation can produce acetylcholine (Ach) and could be beneficial to the patients. Primary fibroblast cell line genetically engineered to express choline acetyltransferase showed the capacity to produce Ach after transplantation into the hippocampus of rats [94]. Another example of the use of the facilitation of genetherapy for AD is the over expression of neprilysine (NEP), an Aβ degrading protease that has been shown to ameliorate extracellular amyloids [95].

Transgenic mice (APP/PS1) injected with lentiviral vector expressing NEP showed a reduction in Ab deposits [96], and MSCs overexpressing the NEP gene demonstrated the ability to degrade Aβ peptides *in vitro* [97]. Similar results were obtained *in vivo* with transgenic mice that were transplanted with fibroblasts engineered with lentivirus carrying NEP [98].

Recently we have created modified neural stem cells which can differentiate, produce dopamine, BDNF/GDNF [99-101]. Our notion, therefore, is that the cell-replacement therapy of AD/PD/Dementia patients with modified neural cells could be relevant [102-106].

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Authors' Contribution

Both the authors have contributed equally to preparing this article, reading, and approving the final manuscript.

Conflict of Interests

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Consent for Publications

Both the authors have agreed to submit this paper for publication.

Ethical Approval

Not applicable.

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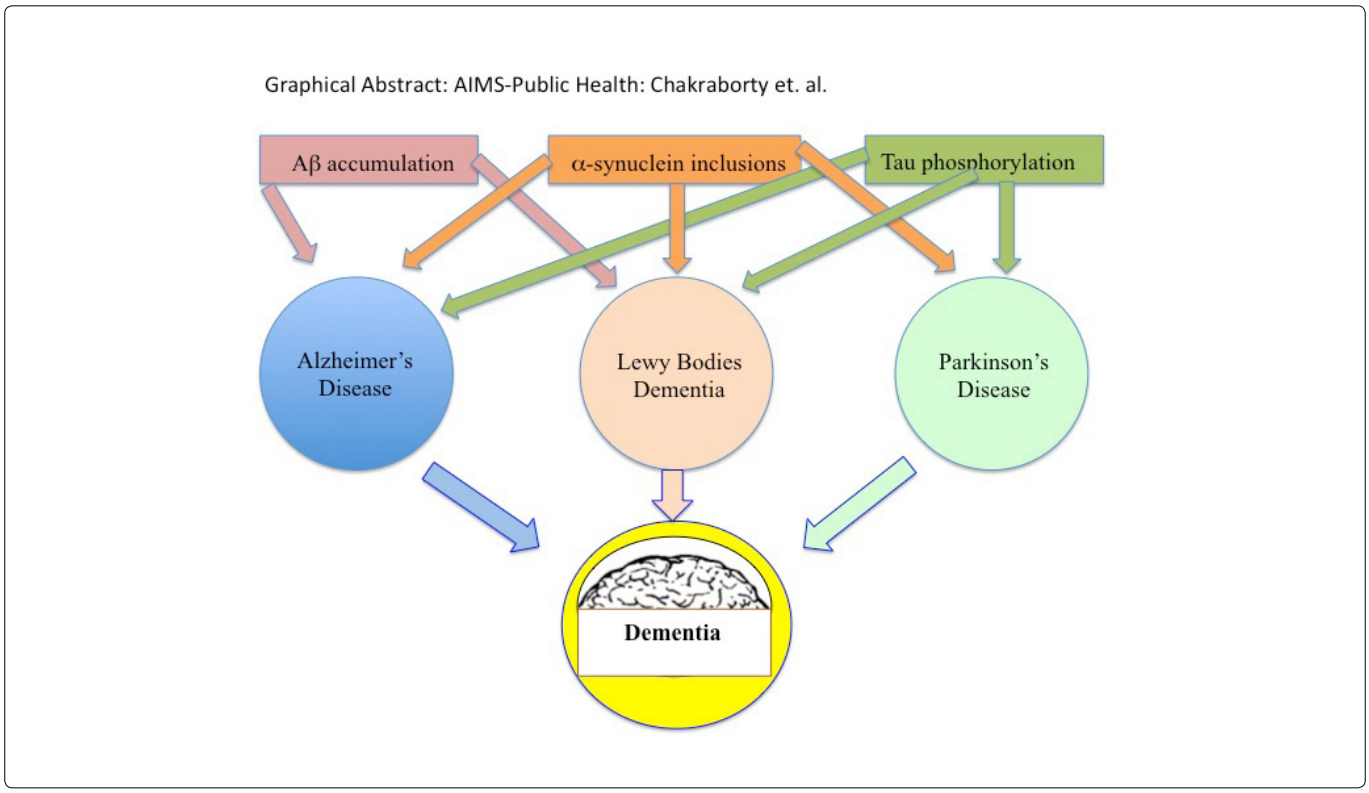
Graphical Abstract



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