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REVIEW

An overview on the correlation of neurological disorders with cardiovascular disease

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Abstract Neurological disorders (NDs) are one of the leading causes of death especially in the developed countries. Among those NDs, Alzheimer's disease (AD) and Parkinson disease (PD) are heading the table. There have been several reports in the scientific literatures which suggest the linkage between cardiovascular disorders (CVDs) and NDs. In the present communication, we have tried to compile NDs (AD and PD) association with CVDs reported in the literature. Based on the available scientific literature, we believe that further comprehensive study needs to be done to elucidate the molecular linking points associated with the above mentioned disorders.

Abbreviations: AD, Alzheimer's disease; Aβ, β amyloid; PD, Parkinson disease; L-DOPA, L-dihydroxyphenylalanine; LBs, Lewy bodies; DA, dopamine; APP, amyloid precursor protein; CVD, cardiovascular disease

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1. Introduction

Alzheimer's disease (AD) is one of the major neurodegenerative disorders, encountered by more than 35 million people worldwide in the year 2010 (Prince et al., 2013). It has been placed 6th leading cause of death in the US only, with an affected population of 5.4 million in the year 2012 (Alzheimer's-Association, 2012; Jabir et al., 2014).

Several studies reported occurrence of synaptic loses, prior to the actual clinical outcome of many neurodegenerative disorders. Scientific reports had also listed some common set of molecular pathological events which lead to the synaptic loss viz. accumulation of certain oligomeric neurotoxic species like β amyloid (Aβ), α-Synuclein and Tau, at different parts of the brain (Crews and Masliah, 2010; Hilton et al., 2013; Milnerwood and Raymond, 2010). The pre-fibrillar forms of the above mentioned proteins especially β amyloid are the precursor of immunological triggers, oxidative stress and apoptosis (Stefani and Dobson, 2003). These oligomers can also interfere with the normal plasticity of the synapse by interrupting nutrient channels inside the neurons, axonal transport of synaptic vesicles, impairing mitochondrial functions and triggering glutamate excito-toxicity (Crews and Masliah, 2010; Crouch et al., 2008). The normal housekeeping machineries fail to clear the above mentioned oligomeric peptides in most of the neurodegenerative conditions, which leads to unbalanced production to clearance ratio (Deane et al., 2009; Gillis et al., 2013).

Genetic inheritance in case of AD has been suggested *via* mutation at three genes present on chromosome 21, chromosome 14 and chromosome 1, coding for amyloid precursor protein (APP), presenilin 1 and presenilin 2 proteins respectively (Alzheimer's-Association, 2013; Zekanowski et al., 2003). Certain risk factors like familial history, metabolic syndrome, presence of ApoE4 allele, brain trauma, education, social and cognitive engagement have also been highlighted in the scientific literature which promote AD onset at earlier ages (Alzheimer's-Association, 2013; Rovelet-Lecrux et al., 2007).

Recently, number of *in vivo* and *in vitro* studies targeted different enzymes and other cellular signaling molecules such as caspase 2, protein phosphatases, fyn kinase, glycogen synthase kinase-3β for the alleviations of AD pathology (Braithwaite et al., 2012; Farr et al., 2014; Jabir et al., 2014; Pozueta et al., 2013; Schenone et al., 2011).

Parkinson disease (PD) is the second most prevalent age-related neurodegenerative disorder after AD, with worldwide occurrence (Khan et al., 2012; Tabrez et al., 2012). Annually, approx 630,000 people are diagnosed with PD in the US alone. Moreover, the projected jeopardy associated with this disorder only from Western Europe is expected to reach 10 million by 2030 (Dorsey et al., 2007; Kowal et al., 2013).

It is a chronic disorder caused by the progressive neurodegeneration in the dopaminergic neurons of substantia nigra resulting in diminished striatal dopamine, which is directly associated with tyrosine hydroxylase mediated production (Tabrez et al., 2012). PD is also characterized with several motor and non-motor deficits along with impaired cognitive, autonomic as well as psychiatric symptoms (Ferrer et al., 2012). The well known clinical symptoms of PD include tremor, muscle rigidity, loss of muscle coordination and bradykinesia (Tabrez et al., 2012). Secondary manifestation like dementia, psychiatric issues, visual hallucinations and depressions may also appear in some cases (Pankratz et al., 1993; Samii et al., 2004).

Depending upon the clinical onset, PD is categorized as juvenile onset PD (the clinical symptoms develop within 20 years), early onset PD (developed before 50 years of age) and late onset PD (developed after the age of 50) (Brüggemann and Klein, 1993; Lücking et al., 2000; Payami et al., 2002).

Inclusion bodies filled with α-Synuclein (an oligomeric protofibril) are known as Lewy bodies (LBs) and their presence is one of the pathological features of PD (Ferrer et al., 2012; Lotharius and Brundin, 2002). α-Synuclein has also been reported to be genetically related with PD onset and also propagate the disease to the neighboring cells (Stefanis, 2012; Tabrez et al., 2012).

An earlier study on transgenic mouse expressing human α-Synuclein suggested the combined role of inclusion bodies and ubiquitin in the immunological events, which leads to dopaminergic terminal loss (Masliah et al., 2000). Very recently, Spinelli et al. (2014) reported over expression of α-Synuclein protein aggregates at the presynaptic terminals in the mouse model construct (Spinelli et al., 2014).

It has been suggested in the literature that hereditary chances of PD occurrence increase 2–3-folds in the immediate relatives of PD patients (Lesage and Brice, 2009; Warner and Schapira, 2003). Several genetic mutations have been reported in different ethnic groups and families of PD patients. However, only two types of genetic carryover have been depicted and the genes associated with that have been mapped (Lesage and Brice, 2009). Autosomal dominant PD have been reported to possess mutations at LRRK2 (PARK8), SNCA (PARK1), UCHL1 (PARK5) and LRRK2 (PARK8) genes, whereas autosomal recessive PD have been reported to have mutations at PARK2 (PARK2), PARK7 (PARK7) and PINK1 (PARK6) genes (Klein and Westenberger, 2012; Lesage and Brice, 2009).

Certain mutation in other genes also increases the risk of PD development. The individuals afflicted with Gaucher's disease caused by the mutation in GABA gene coding for lysosomal housekeeping enzyme beta-glucocerebrosidase, have higher chances of developing PD (Neumann et al., 2009;