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.

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Contents

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;

Shachar et al., 2011). Currently, scientific community is mainly focusing toward disturbed intracellular protein equipoise, mitophagy disturbances and oxidative stress to understand the pathological and genetical aspects associated with PD (Khan et al., 2012; Li et al., 2013; Szeto, 2006).

Cardio vascular disease (CVD) is the end result of the accumulation of atheromatous plaques within the walls of the coronary arteries and remains the principal cause of death worldwide (Braunwald, 1997; Murray and Lopez, 1997). The pathogenic components of atherogenesis have not been completely elucidated. However, epidemiological studies have identified a number of risk factors viz. family history, smoking, hypertension and elevated serum cholesterol levels associated with CVD. There is also extensive evidence of the role of genetic factors in the familial aggregation of CVD and its predictors (Yousefi et al., 2006). Although, there is no doubt as to the role of genetic background in CVD, external factors are also known to play a particularly important part. According to present trends in the US, half of healthy 40-year-old males and one in three healthy 40-year-old women will develop cardio heart disease in future (Alberti-Fidanza et al., 1994). It is the leading cause of death of American women, accounting for 32% of all deaths per year (Berdowska and Zwirska-Korczala, 2001; Hannonen et al., 1986).

Cardiac failure is often associated with an elderly onset of PD and its prevalence has been suggested, twice compared with normal population (Zesiewicz et al., 2004). Though brain and heart tissues vary a lot in their structure and function, their unique high energy demand makes them rely on mitochondrial energy packs (Hemmer and Wallimann, 1993; Mourier et al., 2014). Despite the highest number of mitochondria, both cardiomyocytes and neurons lack mitotic properties and fail to spot mitochondrial damage (Bhandari et al., 2014). Recent findings depicted the association of mitofusin 2 (Mfn2, a key functional element in heart mitophagy) with two other PD associated factors, viz. PINK1 and Parkin (Chen and Dorn, 2013). Any genetic or physiological defects in Parkin-mediated mitophagic signaling, impair removal of damaged mitochondria and affect both the brain and heart. Mitochondrial dysfunction and the mishandling/perturbed degradation of proteins have both been implicated in the loss of dopaminergic neurons (Gegg et al., 2010). There has also been reports that PTEN-inducible kinase 1 (PINK1)–Parkin mitochondrial quality control pathway is associated with both PD and heart function. Another cardinal feature in PD is orthostatic hypotension (OH), which is referred as consistent fall in both systolic as well as diastolic blood pressures. Approximately 30–40% of PD patients exhibit this phenomenon and most of them have been observed with cardiac nor-adrenergic denervations (Goldstein, 2006; Jain and Goldstein, 2012).

In a recent study, PD patients reported an increased risk of ischemic stroke along with other co-morbidities like coronary heart disease, hypertension, and other heart diseases (Huang et al., 2013). There have also been reports that PD treatment by the widely used dopamine agonists pergolide and cabergoline causes heart valvulopathy (Massel and Suskin, 2007). The above mentioned findings clearly suggest a possible association between CVD and PD.

Growing evidence also supports a strong association between cardiovascular disease (CVD), and higher risk of dementia and AD (Rusanen et al., 2011; Stampfer, 2006). Several linking features such as hypoxia, amyloid-beta and oxidative stress had been proposed as a connecting point between AD and CVD. Both of these diseases could be considered as vascular disorders because of lack of optimal blood flow in both the brain and heart. The hypoxic events in the brain triggers increased amyloid-beta deposition and plaque formation in central neurons (Sun et al., 2006). Moreover, ischemic lesions could affect specific neuronal networks and also trigger inflammatory host response, which leads to the neuronal degeneration (Casserly and Topol, 2004). The above mentioned hypoxic events could promote the development of AD as it results in heart diseases. Certain genetic factors like Apo E4 carriers are more vulnerable to AD or dementia compared with CVD (Kivipelto et al., 2008; Martins et al., 2006). Impaired cognitive functions have been reported in case of ischemic and atherotic individuals (Dardiotis et al., 2012). The functional deficits due to atrial fibrillation, coronary artery disease, aortic or mitral valve diseases reduce the cerebral blood flow, which leads to exaggerations in cognitive function arising due to the excess cerebral accumulation of tau or Aβ deposits (Bell and Zlokovic, 2009; Hakim et al., 2013).

Recently, compiling data from large scale genome wide association studies on AD pathogenesis, researchers had concluded the involvement of cardiovascular disease pathway in AD (Liu et al., 2014). These findings clearly show a strong association between AD and CVD.

2. Conclusion

Based on our manuscript, it is quite clear that CVD are associated with neurological disorders especially AD and PD. However, a lot of work needs to be done before finding out the exact linking point among these diseases.

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