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Parkinson`s disease and emerging of imaging tools for prognosis and diagnosis applications

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ABSTRACT

Parkinson's disease (PD) is a chronicdegenerative neurological disease, characterized by a range of motor (bradykinesia, rigidity, and tremor) and non-motor (fatigue and depression) symptoms in PD, each of which will affect a particular patient to varying degrees in the limbs resulting in the postural instability. A clearer explanation of the association of nondopaminergic structures with PD, could potentially provide valuable insight into non-motor symptoms experienced by subgroups of cases and hopefully rationalize the therapeutic options for the management of these disabling complications.

KEY WORDS: Parkinson's disease, Alzheimer disease, MRI, PET, MRS, DWI, DTI

1. INTRODUCTION

Epidemiology and clinical manifestation: Parkinson's disease (PD) is a disablingchronic neurological disease, characterized by a range of motor (bradykinesia, rigidity, and tremor) and non-motor (e.g., tiredness and depression) symptoms in PD, each of which will influence a particular patient to a different degrees in the limbs followed by postural unstability (McNaught, 2004). The disease is uncommon before the sixth decade and the prevalence rates increase with age. Furthermore, after Alzheimer disease (AD), Parkinson's disease is the most common neurodegenerative disease (Ghannad, 2016), which has high annual economic costs. In our increasingly ageing society, the prevalence of PD and the related pressure put on health-care systems are projected to grow substantially in the coming years. The incerasing loss of dopamine neurons in the substantia nigra SN and the subsequent dopaminergic denervation in forebrain areas are the main neuropathological characteristic of PD (Teismann, 2003). By the time a patient is diagnosed with PD, 30–50% of nigrostriatal neurons might have already been lost, representing striatal dopamine loss of nearly 80%. However, PD pathogenetic processes include the dopaminergic system, diffuse pathology affects other, nondopaminergic, systems such as the serotonergic, glutamatergic, opioid, cannabinoid and cholinergic systems. Results from seven population-based studies performed in European countries suggest that the overall prevalence of PD in people aged over 65 is 1.8%, with an increase from 0.6% for persons aged 65 to 69 years to 2.6% for people aged 85 to 89 years. Progression of symptoms in PD may occur over 10–30 years but can be accelerated in some individuals. Moreover, While PD is characterized by the abnormal deposition of α-synuclein in multiple brain regions, the brunt of the pathology ending in the principal features in the ventrolateral tier of the SN pars compacta (SNc). The formation of proteinaceous intraneuronal Lewy body inclusions, Lewy neurites and progressive neuronal loss particularly targeting the substantia nigra are the cardinal pathological feature of the disease. Based on this observation *Braak et al.* have proposed a six point staging procedure for the pathological process in PD. They reported that in stage 1 Lewy body pathology appears in the medulla oblongata and olfactory structures and spreads to the pons by stage 2. During stage 3, the SN and midbrain brain nuclei are influenced, and limbic areas are impressed in stage 4. Eventually, in stages 5 to 6, the inclusions seemto be in the neocortex. Despite these findings of widespread Lewy body disease, the symbol of PD pathology is the loss of the dopaminergic neurons in the SNc which results in striatal dopamine deficiency. This in turn leads to increased inhibitory output activity from the basal ganglia to the ventral thalamus and frontal cortex and subsequent development of Parkinsonism. When 80% of striatal dopamine and 50% of the nigra compacta cells have been vanished classical PD symptoms occur (Desikan, 2006). Over the past two decades, neuroimaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) are widely used to diagnose PD and elucidate the neuropathological mechanisms and compensatory responses underlying symptoms and treatment associated complications, and to monitor disease progression in vivo. MRI provides insights into brain structures, and presents essential and important information such as the brain volume and tissue content (Desikan, 2006). It facilitates not only the diagnosis, but also the understanding of disease process in movement disorders. Though, advances in structural and functional imaging have improved the capacity of MRI to detect changes in PD as well as to differentiate between PD (Fatehi, 2016). MRI has provided several candidate biomarkers that have a potential to inform on the disease process. Biomarkers are quantitative characteristics which are used as indicators of biological or pathological states. In neuroimaging, biomarkers are measures derived from images that reflect the presence of diseases or their severity and that can be used for early diagnosis, prognosis or to monitor responses to therapeutic interventions (Rahmani Tanha, 2016). Biomarkers are expected to detect early neuropathological features

and mechanisms underlying neurodegeneration in PD and to correlate with disease progression in order to allow the monitoring of disease status. Ideally, they should be able to detect preclinical changes. Reliable biomarkers need to be confirmed by independent studies. Promising candidate biomarkers were able to detect changes at various levels of the central nervous system, including the SN, the brainstem, the basal ganglia and the cortex. Conventional MRI may aid in the differentiation of atypical Parkinsonism (Fatehi, 2016). The presence of the ''hot-cross bun'' sign (arising from a combination of atrophy and increased signal) in the pons, putaminal atrophy, and a hyperintense rim at the edges of the putamen suggest a diagnosis of multiple system atrophy (MSA), whereas the presence of midbrain atrophy with dilatation of the third ventricle is more likely associated with chronic supranuclear palsy (PSP). However, most of these signs lack sensitivity, and by themselves, are not specific. A hyperintense rim at the boundaries of the putamen and mild degree of putaminal hypodensity was described in specialtypes of Parkinson's disease (PD). Volumetric analysis may better discriminate PD from atypical Parkinsonism. MSA patients have smaller striatal and brainstem volumes compared with PD patients. Using voxel-based morphometry, Brenneis (2003) showed cortical atrophy in MSA patients compared to PD and control subjects. There was also significant reduction in volume of the left caudate head in PD patients compared with control subjects. Others have demonstrated significant atrophy in the anterior cingulate gyrus, hippocampus, and superior temporal gyrus in PD patients. Demented PD patients had several cortical and subcortical areas affected, but the most significant change was in the anterior cingulate gyrus, hippocampus, and thalamus. In addition, MRI is more common and available in clinical practice compared to PET and SPECT and is widely used to differentiate idiopathic PD from secondary causes of Parkinsonism such as vascular disease and other structural lesions. MRI findings can also discriminate PD from multiple system atrophy through appearing a reduced T2-weighted Putman signal, and PSP and cortical-basal degeneration by revealing midbrain and cortical atrophy. There is an abundance of papers published on this topic, but they are beyond the scope of the current review and will not be discussed here further. Conventional MRI as standard method is generally used in patients with idiopathic PD without dementia, it is quite difficult to detect definiteirregularity in the basal ganglia structures. Several studies have investigated the application of MRI sequences designed to indicate the changesin midbrain iron content as post-mortem studies in PD. They reported an increase in iron concentration in the SN. Early MRI studies failed to show significant differences in SN iron levels between PD patients and controls. The visualization of the SN and other brainstem nuclei have been increased with the coming of new MR contrasts and image analysis techniques. Cortical lesions can be followed using various techniques that can detect changes in the thickness, volume and density of grey matter in the cortex. Also, new MRI techniques, yet, seems to be more sensitive to iron increases in PD patients. Structural changes can be detected in the SN of PD patients using inversion recovery white and grey matter signal-suppression sequences, also in the early stages ofthe disease, with significant dissimilarities between patients and control group (Radulovic, 2004).

Role of advanced MRI techniques in PD:

Magnetic resonance spectroscopy (MRS): Proton MRS (^{1}HMRS) as a non-invasive imaging technique is commonly sued to provide in vivo of intracellular metabolic status, and can be used as a neuroimaging biomarker for normal biological and pathological processes or response to a therapeutic intervention. MRS allows the in vivo measurement of brain metabolism (Fatehi, 2016a). Four major hydrogen-containing metabolites may be identified: a) Nacetylaspartate (NAA), a marker of neuronal integrity; b) creatine (Cr), which relates to general metabolism; c) choline (Cho), which is altered by membrane turnover; and d) myoinositol (MI), a marker of glial cells. There was a widespread reduction in NAA=Cr ratio in the pons, putamen, and cortical white matter in MSA patients compared to control subjects, representing widespread neuronal and axonal involvement. Compared to PD patients, MSA patients had significantly reduced NAA=Cr ratio in the pons and putamen. Of interest, the pontine NAA=Cr ratio was reduced in MSA patients even in the absence of structural MRI findings such as the ''hot-cross bun'' sign and putaminal rim hyperintensity. In the substantia nigra (SN) of PD patients both increased and decreased NAA= Cr ratios were reported (Szczepaniak, 2005). Quantitative analysis confirmed no significant difference in MRS metabolites between PD and control subjects, except for a reduction in CSF-corrected creatine in the SN of PD patients. According to the results obtained from ^{1}HMRS spectra, there was an increase in NAA/Cho ratios in the lentiform nucleus of PD patients in comparison to control group. *Choe et al.* demonstrated that there is an asymmetric decrease in NAA/Cr ratios in the contralateral SN compared to the symptomatic side in PD with unilateral symptoms. Yet, a significant increase was reported in total Cr levels in prefrontal cortex, but there was no change in NAA and Cho in SN of PD patients (Pettegrew, 1991). Other studies reported metabolic alterations also in cortical structures. Reduced NAA and Cho levels in temporoparietal cortex and reduced NAA levels in motor cortex, and posterior cingulated cortex were observed. It was reported in several studies that there is no difference in the metabolite between the PD patients and the control group in either metabolite ratios or absolute concentration of NAA, Cho, and Cr in cortical-basal ganglia loop. Recently studies shows that a statically significant differences were not observed between PD patients and control group of NAA, Cho, and Cr ratios in brainstem, caudate, thalamus, lentiform nucleus, and association cortices. These results are inconsistent with single-voxel ^{1}HMRS studies that

showed no significantly reduced NAA in lentiform nucleus and putamen and thalamus. Notable changes in neurochemical levels may demonstrate the pathophysiological mechanisms underlying of PD. Reducing NAA levels in all cerebral structures of PD patients by ^{1}HMRS, indicates wide neuronal degenerations, which involves the corticobasal ganglia-thalamocortical networks, but also metabolic dysfunctions. Indeed, the decrease of PD would confirm the hypothesis that the dysfunction of the mitochondrial electron transport chain is a primary or secondary event in PD pathogenesis, due to NAA is synthesized in neuronal mitochondria in an energy-dependent manner. Although the reduction of NAA levels is a condition that may occur also in other neurodegenerative diseases, this result obtained from PD patients might indicate the defects or injuries in mitochondrial metabolic system that hypothetically contribute to neuronal deterioration. The mitochondrial dysfunction in PD is also supported by a recently study that reported in occipital lobe of PD patients high levels of Lac, metabolite which accumulates in most disease associated with a deficiency in mitochondrial oxidative metabolism (Ciurleo, 2014).

Diffusion-weighted imaging (DWI): New diffusion techniques particularly DWI is a relatively new method that measures the diffusion of water molecules in tissue. Water molecules tend to diffuse along the directions of the fiber tracts in the brain. Any disruption of tissue architecture will increase the freedom of diffusion of water molecules, leading to greater diffusion isotropy. Quantification of diffusion is possible by calculating the apparent diffusion coefficient (ADC). DWI requires a very short acquisition time and has relatively high spatial resolution. In recent years, investigators have applied DWI technology to define areas of neuronal loss in neurodegenerative diseases. MSA patients have significantly higher putaminal ADC values reflecting the greater neuronal loss in this region compared to PD and control subjects. However, there was no significant difference in ADC values between PD and control subjects. PSP patients have higher ADC values in the putamen, caudate and globus pallidus compared to PD patients, but a significant difference in ADC values between PSP and MSA patients was not present. Nevertheless, using a step-wise logistic regression analysis, the authors found that putaminal ADC was able to discriminate between PSP and PD with a sensitivity of 90% and a positive predictive value of 100%. In another DWI study, there was a significant increase in ADC values in PSP patients compared to controls in the prefrontal and precentral white matter (Fattahi, 2009).

Diffusion tensor imaging (DTI): DWI measures the diffusion of water molecules in one plane, and may underestimate the diffusion-related pathologic process in the brain (Au, 2006). A modified technique, known as diffusion tensor imaging (DTI), allows the ADC in three orthogonal directions to be calculated and averaged as the diffusion tensor Trace (D) (Gharib Salehi, 2016). According to the *Schocke et al.* studyin the putamen and pallidum of MSA patients *a*n obvious increase was observed in Trace (D) compared to PD patients. Moreover, in MSA patients, a significant increase was observed in putaminal ADC in the y- and z-directions. The putaminal Trace (D) completely distinguished MSA patients from PD and control group. *Yoshikawa et al. (2004)* reported early changes in the nigrostriatal projections in parkinsonian brains by another measure of diffusion identified as fractional anisotropy (FA). They reported a reduction in FA values in PD patients compared to control subjects, in regions of interest placed along a line from the SN to the lower part of the striatum. In advanced cases of PD, the FA values were also reduced in the subcortical white matter. PSP patients had reduced FA values in most subthalamic structures and in subcortical white matter. DTI and diffusion tensor tractography (DTT) are promising and new methods of MRI investigating the integrity of tracts in white matter and, indirectly, neuronal connectivity in the brain. Generally, in the brain tissue water diffusion is constrained along nerve fibers and so is anisotropic. Degeneration of tracts leads to the loss of this directionality of diffusion or anisotropy. DTI measures the direction and magnitude of diffusivity of water molecules in tissues and can be used as an index of damage to neuronal tracts. There are two main quantities of interest inclusive of the mean apparent diffusion coefficient (ADC) (for measuring total molecular motion averaged over all directions) and fractional anisotropy (FA), (as a measure of the directional diffusivity of water). DTT is a computational method that restructures major fiber bundles in the brain based on the anisotropy of water movement in myelinated white matter. *Yoshikawa et al.* and *Chan et al.* have reported lower values of FA in the SN of PD patients compared to controls. FA values were inversely correlated with disease severity. DTI has also provided new insights into the pathologic process in idiopathic dystonia. Furthermore, advances in MR imaging have however shown significant promise. Fractional anisotropy (FA) is reduced in the caudal SN and it is also possible using MR to detect changes in the shape of subcortical structures. In the frontal lobes FA is considered abnormal, genu of the corpus callosum and superior longitudinal fasciculus of PD subjects. Multimodal imaging combining R* (iron deposition) and FA in the substantia nigra with mean diffusivity measures in the striatum display a mainlygreat potential to discriminate PD subjects from controls (Assaf and Pasternak, 2008).

2. CONCLUSION AND PERSPECTIVES

PD is a neurodegenerative disease, which insidious can cause difficulties in its early diagnosis. This is important toslow down the disease progression and optimize the therapy. In recent decades, considerable progresses has been achieved in the detecting and assessment of potential biomarkers for the early differential diagnosis and monitoring treatment efficacy. Neuroprotection is still a challenge in PD studies. It seems that in the near future novel putative

neuroprotective agents will become available which will require testing. Current imaging biomarkers have been established as an important addition to clinical information for assessing both mechanism and effectiveness of neuroprotective agents but they have also shown on occasion discordance with clinical outcome. Further research should aim to determine direct drug effects on the imaging biomarkers currently available but also to develop new imaging techniques to longitudinally monitor improvement and treatment of PD. Advancein thenovel radiotracers to target non-dopaminergic brain pathways and the glial reaction to disease is also required. A wellrecognition of the connection of nondopaminergic structures in PD could potentially provide insight into non-motor symptoms experienced by subgroups of patients and hopefully rationalize the treatment methods for the control of these disabling complications.

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