Magnetic resonance imaging as a potential biomarker for Parkinson's disease

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Although a magnetic resonance imaging (MRI) biomarker for Parkinson's disease (PD) remains an unfulfilled objective, there have been numerous developments in MRI methodology and some of these have shown promise for PD. With funding from the National Institutes of Health and the Michael J Fox Foundation there will be further validation of structural, diffusion-based, and iron-focused MRI methods as possible biomarkers for PD. In this review, these methods and other strategies such as neurochemical and metabolic MRI have been covered. One of the challenges in establishing a biomarker is in the selection of individuals as PD is a heterogeneous disease with varying clinical features, different etiologies, and a range of pathologic changes. Additionally, longitudinal studies are needed of individuals with clinically diagnosed PD and cohorts of individuals who are at great risk for developing PD to validate methods. Ultimately an MRI biomarker will be useful in the diagnosis of PD, predicting the course of PD, providing a means to track its course, and provide an approach to select and monitor treatments. (Translational Research 2016;175:4–16)

Abbreviations: ATP = adenosine triphosphate; BOLD = blood oxygenation level-dependent; Cr = creatine; DAT = dopamine transporter; DTI = diffusion tensor imaging; fMRI = functional MRI; FA = fractional anisotropy; GABA = gamma-aminobutyric acid; Gln = glutathione; (^{1}H) = proton; iRBD = idiopathic rapid eye movement (REM) sleep behavior disorder; LBD = Lewy body dementia; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; MTI = magnetization transfer imaging; NAA = N-acetylaspartate; NAC = N-acetylcysteine; NAD+ and NADH = oxidized/reduced forms of nicotinamide adenine dinucleotide; phMRI = pharmacologic MRI; (^{31}P) = phosphorus; PD = Parkinson's disease; PET = positron emission tomography; QSM = quantitative susceptibility mapping; rsfMRI = resting state functional MRI; RAFF = relaxations along a fictitious field; SN = substantia nigra; SPECT = single photon computed tomography; SWI = susceptibility-weighted imaging

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder associated with the loss of dopaminergic neurons in the substantia nigra (SN), the presence of Lewy bodies (which comprise alpha-synuclein), and gliosis.[1] However, PD involves many other areas besides the nigra.[2,3] Braak et al have proposed that disease may begin in the olfactory system or gastrointestinal tract and then involve the brainstem, subcortical regions, and ultimately the cortex via a process of cell-to-cell transmission of prion-like toxic misfolded alpha-synuclein aggregates.[2-7] The process of disease evolution appears to progress through neuronal pathways that represent connected intrinsic networks.[2,3,8] Presently, there is no accepted biomarker or biomarkers for PD, but the search is ongoing.[1] A biomarker may be defined as an indicator of a pathologic process or a pharmacologic response to a therapeutic intervention.[9] More specifically a biomarker for PD could be used in diagnosing PD (*diagnostic marker*), in predicting the risk of PD or its course once begun (*prognostic marker*), to characterize disease severity (*staging marker*), or to monitor

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disease progression or response to therapy or therapies (*theragnostic marker*).[10] Theragnostic markers represent an important field called theragnostics, whereby molecular diagnostic tests may be linked to targeted therapeutics.[10] To date theragnostics have been primarily limited to the field of cancer, but its role in neurologic disorders may increase with the arrival of nanomedicine and improved understanding of the molecular aspects of brain conditions. For example in PD, theragnostics could be represented by a diagnostic and therapeutic imaging antibody that is directed against abnormal aggregates of alpha-synuclein protein, which is a pathologic hallmark of PD and thought to be intrinsic to disease pathogenesis (hence PD is considered a synucleinopathy). This antibody would not only provide evidence of disease through the use of a contrast agent or a radioligand detected by a brain scan of some sort, that is, positron emission tomography (PET) or magnetic resonance imaging (MRI) scan, but would also aid in treating PD through antibody binding and subsequent elimination of pathogenic factor(s), that is, immunotherapy. However, such a concept remains in the pipeline as researchers are presently focusing on each part separately. Some are developing therapeutic antibodies, that is, active and passive alpha-synuclein immunization studies are in clinical trials and are still unproven, whereas others are focusing on developing alpha-synuclein imaging ligands that could be used with PET scanning.[11,12] Thus, although there is a great hope for theragnostic imaging markers for PD, the greatest advancements in MRI may be in developing biomarkers that aid in the diagnosis, staging, and prognostication of PD. To date there is no established MRI biomarker or biomarkers for PD, but it is clear that further study is needed, especially in a longitudinal fashion.[13] As of 2014, 10 longitudinal MRI studies had been completed in PD, and they were focused on whether there were "structural" changes over time. Since then a few longitudinal MRI studies using nonstructural methods have been published and will be outlined subsequently.[14] To advance the field a recent review by Schuster et al calls for greater collaboration between centers and standardization of methodology to allow for more careful analysis of MRI as a biomarker.[14,15]

However, before discussing MRI methods, it is important to recognize the means by which biomarkers are validated because there is no gold standard to make a diagnosis of PD other than autopsy.[16,17] Hence, a premortem "diagnosis" of PD is made clinically, which has its limitations with ~10% of individuals suspected of having PD have alternative pathologic diagnosis.[16] Additionally, some individuals with clinically defined "PD" may have coincident pathologies with the presence of other degenerative brain disorders in addition to pathologic changes in PD on autopsy.[16] To this point, researchers have shown that some individuals with clinical PD have abnormal amyloid brain PET imaging, supportive of concomitant Alzheimer amyloid pathology.[18] Additionally with the arrival of tau imaging PET ligands, we expect researchers to demonstrate concomitant abnormal tau protein in the brains of people with clinical PD as well. Meanwhile, in another study individuals clinically suspected to have PD did not have a neurodegenerative disorder at all: re-evaluation of these individuals did not show clinical progression, and repeat dopamine transporter (DAT) single photon computed tomography (SPECT) imaging remained normal and did not show typical DAT imaging changes seen in PD.[19] From a clinical point of view, PD is heterogeneous with different etiologic (genetic and environmental) factors as well as varying clinical presentations and different rates of disease progression.[20] Thus, international meetings have focused on genetic, pathologic, or clinical definitions of disease but have not resolved the best way to diagnose PD. In regards to etiology, ~15% of PD is because of dominant or recessive genetic mutations and the remaining ~85% of those affected with PD have incompletely defined genetic-environmental cause(s).[17] Clinically, PD on average begins around the age of 58–60 years but there is a broad range in the onset age; those with an onset less than 30–40 years tend to have a definable genetic basis.[17] Interestingly, a sleep disorder, idiopathic rapid eye movement sleep behavior disorder (iRBD), is one precursor to PD. In individuals with iRBD, there is usually alpha-synuclein pathology in more caudal brainstem regions and ascension of pathologic changes to the regions such as the SN as the disease evolves into PD or other synuclein disorders such as Lewy body dementia (LBD) or multiple system atrophy. Thus, some have proposed longitudinal studies of individuals with iRBD to help identify and validate biomarkers for PD and these other synucleinopathies.[21-24] Ultimately those with PD are diagnosed when there are sufficient motor features that characterize the disease, and these features vary with some having a tremor predominant form of PD, whereas others have primarily slow-stiff features (akinetic-rigid phenotype). The clinical phenotype and age of the onset may portend a different clinical course for affected individuals.[20,25,26] Researchers have also shown that higher serum levels of the antioxidant uric acid are associated with a better clinical course of PD and may be a prognostic biomarker.[27,28]

PD is a complex condition with numerous causes, different clinical phenotypes, varying rates of progression, and *different pathologies—both in distribution*