Neurodegeneration in preclinical stages of Parkinson’s Disease

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Summary
During the preclinical phase of Parkinson’s disease (PD), there is a progressive loss of neurons in the substantia nigra and other nuclei of the brainstem. This progressive neurodegenerative process probably explains that motor and non-motor signs such as sleep disorders, olfactory dysfunction or depression can be identified during this premotor phase of PD before the diagnosis can be made. The investigation of subjects at risk of PD, i.e. presenting these preclinical signs of PD, can be used to study the dynamics of neurodegeneration in PD during its prodromal stages. Another way of studying the dynamics of neurodegeneration in preclinical PD is to study asymptomatic PD-related gene mutation carriers. The identification of subjects in the preclinical stage of PD would allow developing and testing possible neuroprotective therapies. During the preclinical phase of PD, imaging has shown a number of brain abnormalities including dopaminergic striatal dysfunction using radiotracers, increased iron load using transcranial ultrasound and R2* relaxometry, changes in diffusion imaging metrics, structural changes in the cortex, and olfactory regions. Patients with REM sleep behavior disorders have been particularly studied as a window into preclinical PD. Reduced neuromelanin-sensitive MRI signals in the area of the locus coeruleus/subcoeruleus complex, reduced fractional anisotropy in the pontine tegmentum and perfusion changes in the medial temporal lobe were reported in these patients. This presentation will describe the imaging findings that were reported in subjects during the preclinical phase of PD and discuss the potential role of imaging in these subjects.

Introduction
Neurodegeneration in Parkinson’s disease (PD) occurs long before the occurrence of motor symptoms. During this presymptomatic phase, there is a progressive loss of neurons in the substantia nigra (SN) resulting in a deficit in striatal dopamine. Neurodegeneration is also present in other brainstem regions particularly in the medulla oblongata and the pontine tegmentum including the locus coeruleus/subcoeruleus complex and the raphe nucleus (Braak et al. 2003).

The identification of subjects in the preclinical stage of PD is important to understand the dynamics of progression of neurodegeneration in PD and also in view of the possible development of neuroprotective therapies. Such therapies should be more effective if they are applied early in the disease course. The demonstration of efficacy in the clinical phase using motor measures to establish clinical relevance cannot be applied to preclinical PD trials. In preclinical PD, the classical and time-consuming way of demonstrating clinically relevant benefits would be to assess time to motor impairment. Therefore, surrogate markers, such as imaging markers for motor change or progression are needed. Another important role of imaging markers would be sample enrichment in prodromal PD in drug trials. An international multi-center study, the Parkinson Progression Marker Initiative (PPMI), was designed to identify PD progression biomarkers and to improve understanding of disease etiology (http://www.ppmi-info.org).

During the preclinical phase, motor and non-motor signs can be identified several years before the diagnosis of PD can be made. This signs include sleep disorders, olfactory dysfunction, autonomic dysfunction, depression, subtle motor signs such as changes in quantitative motor tests and handwriting, in voice and face akinesia, or reduced arm movement and limb akinesia during gait (Postuma et al. 2012). In particular, rapid eye movement (REM) sleep behaviour disorder (RBD) is an early non-dopaminergic syndrome with nocturnal violence and increased muscle tone during REM sleep that can precede Parkinsonism by several years (Postuma et al. 2014). Patients with idiopathic RBD (IRBD) have been used to assess other prodromal predictors of PD and to follow the evolution of PD from its prodromal stages (Postuma et al. 2014).

Another way of studying the dynamics of neurodegeneration in preclinical PD is to study asymptomatic gene mutation carriers. PD is commonly sporadic but familial forms of the disease are observed in less than 10% of the patients. More than 18 loci have been related to PD and 6 genes identified in these loci have been shown to conclusively cause monogenic PD (Lesage et al. 2012). However, these subjects are very rare and studies reported only a limited number of subjects.

Dopaminergic function
Striatal dopamine changes can be detected using 18F-fluorodopamine (18F-FDOPA) positron emission tomography (PET) or single photon emission computed tomography (SPECT) in subjects “at-risk” of PD.

In PD patients, longitudinal studies showed that the progression of DA dysfunction was best described by an exponential function (Nandhagopal et al. 2009). Early left-right asymmetries of striatal dopaminergic dysfunction were reduced over time whereas the rostral-caudal gradient was maintained. Subclinical deficits of DA function was shown in clinically unaffected twins of PD patients (Piccini et al. 1999), in subjects exposed to nigral toxins (Calnes et al. 1999) and with a family history of inherited PD (Walter et al. 2004, Nandhagopal et al. 2008, Kahn et al. 2005, Binkofski et al. 2007). The meaning of DA dysfunction in these subjects is unclear. PET or SPECT also detected abnormalities of DA function in subjects with hyposmia (Berendse et al. 2001) and RBD (Iranzo et al. 2011).

Iron load
Iron appears to play an important role in the neurodegenerative process, which occurs in the SN (Sian-Hulsmann et al. 2011). Iron load can be estimated by using different imaging techniques such as transcranial sonography (TCS) and MR relaxometry.

Trancranial sonography. Using TCS, hyperechogenicity has been evidenced in IPD in the area of the SN (Berg et al. 2002). SN hyperechogenicity has been related to increased iron load (Berg et al. 2002). In genetic PD, TCS studies generally showed an increase in SN echogenicity (Brockmann et al. 2011, Bruggemann et al. 2011). In healthy subjects older than 50 years, the presence of SN hyperechogenicity was associated with demonstrated
olfactory dysfunction and mild motor impairment (Liepelt-Scarfone et al. 2011). Subjects with SN hyperechogenicity exhibited higher association with premotor biomarkers.

R2* relaxometry. MR relaxometry is based on the measurements of T2* relaxation times and R2* relaxation rates (Ordidge et al. 1994), which correlate with iron content in primates (Hardy et al. 2005) and in human postmortem studies (Langkammer et al. 2010). R2* values are increased in PD (for review see Lehericy et al. 2012). Recently, similar increased in R2* was reported in symptomatic as well as asymptomatic LRRK2 and Parkin mutation-carrying patients suggesting increased high iron these subjects (Pyatigorskaya et al. submitted).

Other MRI markers. Fractional anisotropy using diffusion imaging and magnetization transfer are also reduced in the SN of PD patients (for review see Lehericy et al. 2012) but the progression changes of these markers remains to be investigated in preclinical PD.

Depression
Depression in PD patients was associated with structural changes in the limbic system including medial, orbitofrontal and temporal regions (Kostic et al. 2010) and the mediadorsal thalamus (Cardoso et al. 2009).

REM sleep behavior disorders
RBD can precede Parkinsonism by several years (Postuma et al. 2014). RBD may appear in subjects without any other neurological disease (idiopathic RBD or IRBD). Patients with IRBD have increased risk of developing PD, dementia with Lewy bodies (DLB) and multiple system atrophy, with a rate of conversion of about 50% within 5 years (Boeve et al. 2007; Iranzo et al. 2006).

Diffusion imaging. In IRBD, diffusion MRI changes were localized in the midbrain tegmentum, SN area, rostral pons and pontine reticular formation (Scherfler et al. 2010, Unger et al. 2010, Garcia-Lorenzo et al. 2013). These data are in line with a brainstem origin of neurodegeneration in IRBD. Neurlemelanin imaging. In PD, the neuronal origin of RBD has recently been more precisely related to neurodegeneration in the locus coeruleus/subcoeruleus complex in the pontine tegmentum (Garcia-Lorenzo et al. 2013). This complex contains neurons that present a pigment, neuromelanin (Baker et al. 1989). Neurlemelanin is paramagnetic with short T1 relaxation time when combined with metals (Enochs et al. 1997) leading to bright signal intensity in healthy human subjects (Keren et al. 2009). Signal intensity was reduced in PD in this area and correlated with muscle tone during REM sleep (Garcia-Lorenzo et al. 2013).

Temporal perfusion. Temporal perfusion (regional cerebral blood flow) studied using 99mTc-ECD SPECT identified patients with IRBD at risk for conversion to PD or DLB in a 3-year follow-up study (Dang-Vu et al. 2012). High levels of perfusion in the hippocampus at baseline predicted disease progression to Parkinsonism in these subjects. Moreover, hippocampal perfusion correlated with motor and color vision scores in patients.

Olfactory dysfunction and color vision
Olfaction and color vision were also associated with increased risk of developing Parkinsonism and dementia in IRBD patients (Postuma et al. 2011). Abnormalities were measurable about 5 years before disease onset, and progressed slowly in the preclinical stages. In PD patients, olfactory dysfunction was related to atrophy in olfactory regions of the limbic and paralimbic cortex including the right piriform cortex and the right amygdala (Wattendorf et al. 2009). Deficits in color vision in PD patients were associated with white-matter abnormalities evidenced using diffusion imaging in right posterior brain regions (Bertrand et al. 2012).

References