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 proabably 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 been 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 motion 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 trancranial 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 mediodorsal 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.

Neuromelanin 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). Neuromelanin 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. Mov Dis 2012).

References

1. Baker KG, Tork I, Hornung JP, Halasz P. The human locus coeruleus complex: an immunohistochemical and three dimensional reconstruction study. Exp Brain Res 1989; 77: 257-70.
2. Berendse HW, Booij J, Francot CM, Bergmans PL, Hijman R, Stoof JC et al. Subclinical dopaminergic dysfunction in asymptomatic Parkinson's disease patients' relatives with a decreased sense of smell. Ann Neurol 2001;50:34-41.
3. Berg D, Roggendorf W, Schroder U, et al. Echogenicity of the substantia nigra: association with increased iron content and marker for susceptibility to nigrostriatal injury. Arch Neurol 2002;59:999-1005.
4. Bertrand JA, Bedetti C, Postuma RB, Monchi O, Génier Marchand D, Jubault T, Gagnon JF. Color discrimination deficits in Parkinson's disease are related to cognitive impairment and white-matter alterations. Mov Disord. 2012 Dec;27(14):1781-8.
5. Binkofski F, Reetz K, Gaser C, et al. Morphometric fingerprint of asymptomatic Parkin and PINK1 mutation carriers in the basal ganglia. Neurology 2007;69:842-850.
6. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 2007; 130: 2770-88.
7. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24: 197-211.
8. Brockmann K, Groger A, Di Santo A, et al. Clinical and brain imaging characteristics in leucine-rich repeat kinase 2-associated PD and asymptomatic mutation carriers. Mov Disord 2011;26:2335-2342.
9. Bruggemann N, Hagenah J, Stanley K, et al. Substantia nigra hyperechogenicity with LRRK2 G2019S mutations. Mov Disord 2011;26:885-888.
10. Calne DB, Langston JW, Martin WR, Stoessl AJ, Ruth TJ, Adam MJ et al. Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. Nature 1985;317:246-8.
11. Cardoso EF, Maia FM, Fregni F, Myczkowski ML, Melo LM, Sato JR, Marcolin MA, Rigonatti SP, Cruz AC Jr, Barbosa ER, Amaro E Jr. Depression in Parkinson's disease: convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. Neuroimage. 2009 Aug 15;47(2):467-72.
12. Dang-Vu TT, Gagnon JF, Vendette M, Soucy JP, Postuma RB, Montplaisir J. Hippocampal perfusion predicts impending neurodegeneration in REM sleep behavior disorder. Neurology. 2012 Dec 11;79(24):2302-6.
13. Enochs WS, Petherick P, Bogdanova A, Mohr U, Weissleder R. Paramagnetic metal scavenging by melanin: MR imaging. Radiology 1997; 204: 417-23.
14. García-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, Leu-Semenescu S, Gallea C, Quattrocchi G, Pita Lobo P, Poupon C, Benali H, Arnulf I, Vidailhet M, Lehericy S. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain. 2013;136:2120-9.

15. Hardy PA, Gash D, Yokel R, Andersen A, Ai Y, Zhang Z. Correlation of R2 with total iron concentration in the brains of rhesus monkeys. J Magn Reson Imaging 2005;21:118-127.
16. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 2006; 5: 572-7.
17. Khan NL, Scherfler C, Graham E, Bhatia KP, Quinn N, Lees AJ et al. Dopaminergic dysfunction in unrelated, asymptomatic carriers of a single parkin mutation. Neurology 2005;64:134-6
18. Keren NI, Lozar CT, Harris KC, Morgan PS, Eckert MA. In vivo mapping of the human locus coeruleus. Neuroimage 2009; 47: 1261-7.
19. Kostić VS, Agosta F, Petrović I, Galantucci S, Spica V, Jecmenica-Lukic M, Filippi M. Regional patterns of brain tissue loss associated with depression in Parkinson disease. Neurology. 2010 Sep 7;75(10):857-63.
20. Langkammer C, Krebs N, Goessler W, et al. Quantitative MR imaging of brain iron: a postmortem validation study. Radiology 2010;257:455-462.
21. Lehéricy S, Sharman MA, Dos Santos CL, Paquin R, Gallea C. Magnetic resonance imaging of the substantia nigra in Parkinson's disease. Mov Disord. 2012;27:822-30.
22. Lesage S, Brice A. Role of mendelian genes in "sporadic" Parkinson's disease. Parkinsonism Relat Disord 2012;18 Suppl 1:S66-70.
23. Liepelt-Scarfone I, Behnke S, Godau J, Schweitzer KJ, Wolf B, Gaenslen A, Berg D. Relation of risk factors and putative premotor markers for Parkinson's disease. J Neural Transm 2011;118:579–585.
24. Nandhagopal R, Mak E, Schulzer M, McKenzie J, McCormick S, Sossi V et al. Progression of dopaminergic dysfunction in a LRRK2 kindred: a multitracer PET study. Neurology 2008;71:1790-5.
25. Nandhagopal R, Kuramoto L, Schulzer M, Mak E, Cragg J, Lee CS et al. Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. Brain 2009;132:2970-9
26. Ordidge RJ, Gorell JM, Deniau JC, Knight RA, Helpern JA. Assessment of relative brain iron concentrations using T2-weighted and T2*-weighted MRI at 3 Tesla. Magn Reson Med 1994;32:335-341.
27. Piccini P, Burn DJ, Ceravolo R, Maraganore D, Brooks DJ. The role of inheritance in sporadic Parkinson's disease: evidence from a longitudinal study of dopaminergic function in twins. Ann Neurol 1999;45:577-82.
28. Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. Brain. 2012 Jun;135(Pt 6):1860-70.
29. Postuma RB, Gagnon JF, Vendette M, Desjardins C, Montplaisir JY. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder. Ann Neurol. 2011 May;69(5):811-8.
30. Postuma RB. Prodromal Parkinson's disease - Using REM sleep behavior disorder as a window. Parkinsonism Relat Disord. 2014 Jan;20 Suppl 1:S1-4.
31. Pyatigorskaya N, Sharman N, Corvol JC, Valabregue R, Brice A, Lehericy S. Nigral iron deposition in LRRK2 and Parkin mutation carriers using R2* relaxometry. ISMRM conference, Milan, Italy, submitted.
32. Scherfler C, Frauscher B, Schocke M, Iranzo A, Gschliesser V, Seppi K, et al. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. Ann Neurol 2010; 69: 400-7.
33. Sian-Hulsmann J, Mandel S, Youdim MB, Riederer P. The relevance of iron in the pathogenesis of Parkinson's disease. J Neurochem 2011;118:939-957.
34. Unger MM, Belke M, Menzler K, Heverhagen JT, Keil B, Stiasny-Kolster K, et al. Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia nigra, olfactory region, and other brain regions. Sleep 2010; 33: 767-73.
35. Walter U, Klein C, Hilker R, Benecke R, Pramstaller PP, Dressler D. Brain parenchyma sonography detects preclinical parkinsonism. Mov Disord 2004;19:1445-1449.
36. Wattendorf E, Welge-Lüssen A, Fiedler K, Bilecen D, Wolfensberger M, Fuhr P, Hummel T, Westermann B. Olfactory impairment predicts brain atrophy in Parkinson's disease. J Neurosci. 2009 Dec 9;29(49):15410-3.