

EXTRANIGRAL PATHOLOGY AND PREMOTOR DETECTION OF PARKINSON'S DISEASE

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Recently the concept of dividing prodromal Parkinson's disease (PD) into four stages has been proposed. These stages would either precede the motor findings or precede the findings of enough motor signs to be diagnostic of PD. They are:

- 1) Prephysiologic
- 2) Preclinical
- 3) Premotor
- 4) Prediagnostic

It is clear that PD is a neurodegenerative disease that progresses gradually. Currently there are no clearly effective disease-modifying treatments and one reason may be that by the time enough motor signs are present to diagnose PD >60% of the dopamine neurons have been lost. So finding a way to make an earlier diagnosis may be critical to eventually stopping disease progression. As PD has long been thought of as a disease of striatal-nigral dopamine neuron degeneration, establishing that there is extranigral pathology has led to the potential for premotor detection. This talk will discuss potential diagnostic markers in the prodromal stages of PD and the possibility of earlier diagnosis.

Prephysiologic Stage

While the majority of patients with PD do not have a clearly inherited form of the disease, there are a number of genes which have been identified in which mutations either cause PD or increase the risk of developing PD. An autosomal dominant inheritance pattern is seen with mutations and triplication of the synuclein (SNCA) gene and the LRRK2 gene. An autosomal recessive inheritance is seen with mutations of the PARK2, DJ-1 (PARK7), and PINK1 genes. Finally, there are a number of genes found in which mutations appear to increase risk of developing PD including the GBA and UCHL1 genes. The value of these findings are that from the time of birth individuals can be identified who are at risk, they can be followed for potential biomarkers of developing PD, and eventually they could be cohorts to identify disease-modifying treatments.

Preclinical Stage

In this stage the individual has no clinical signs but yet a biomarker might still be found. Currently the main biomarkers being studied are imaging biomarkers. This includes transcranial ultrasound, ¹²³I-MIBG SPECT scans of the heart, radioligand tracer scans of the brain (¹²³I-FP-CIT or DaTScan; ¹⁸F-Dopa or 18F-dihydrotetrabenazine PET scans)

Premotor Stage

Non-motor manifestations of Parkinson's disease (PD) can begin well before motor PD begins. It is now clear, from clinical and autopsy studies, that Lewy type α -synucleinopathy (LTS) is not restricted to the nigrostriatal pathway, and that non-motor manifestations of PD likely arise from a diverse neuroanatomical distribution of LTS.

Incidental Lewy body disease

There are a number of disorders that are neuropathologically found to be synucleinopathies. These include PD, dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and primary autonomic failure (PAF). Additionally, autopsy studies have found that 10-30% of autopsied elderly, with no clinical signs of motor parkinsonism or dementia, have LTS in the brain, and this has been called incidental Lewy body disease (ILBD).

Subjects with ILBD may have been in the prodromal stage of synucleinopathy, and thus, had they lived longer, may have gone on to develop PD, DLB, or MSA. Autopsy studies of ILBD therefore offer a critical opportunity to map the whole-body distribution of clinically prodromal LTS and relate this to non-motor prodromal signs and symptoms.

Autopsy studies have documented the distribution of LTS in both the CNS and PNS of elderly subjects. It has been shown that the olfactory bulb is most likely to be the first-affected brain or body region. Multiple studies have found hyposmia in ILBD and the presence of LTS in the olfactory bulb may be the cause. LTS can also be present in multiple organs outside of the brain, including the heart, GI tract, submandibular gland and skin, and this may play a role in the non-motor complications.

Hyposmia

There are numerous papers that have provided evidence for hyposmia in PD, including pathologically confirmed PD. One hypothesis is that LTS in the olfactory bulb may be the underlying pathology for the hyposmia, while other papers have found a central pathology including LTS in regions of the primary olfactory cortex.

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a sleep disorder characterized by lack of atonia during REM sleep. Multiple studies have shown that RBD is more common in PD than controls with up to 65% of PD patients having RBD. Additionally, idiopathic RBD appears to be a strong risk factor for the development of PD or DLB. Of great interest has been the finding of many non-motor features of PD in the RBD population. Hyposmia is present in RBD and those with both RBD and hyposmia appear to progress to PD or DLB at a faster rate. A second non-motor finding in PD that is also found in RBD is an abnormality in color vision. This may well be due to the presence of synucleinopathy in the retina. The neuropathology underlying RBD is consistent with it being a synucleinopathy. In the few autopsy studies of idiopathic RBD published to date, the presence of LTS suggests a pathologic role.

Constipation

Much has been written in the past few years regarding LTS in the colon, but there have been conflicting reports. As almost all studies have used differing methods and there have been very few replication studies, it is difficult to come to clear conclusions. Findings that have been replicated by multiple groups include a rostral-caudal GI tract gradient of LTS and a greater LTS involvement of the intermyenteric plexus, as compared to the submucosal plexus. Within the CNS there is LTS involvement and neuronal loss in the dorsal motor nucleus of the vagus early in PD and this may also underlie constipation. Finally, LTS in the spinal cord, including the recent findings in the lateral collateral pathway of the sacral spinal dorsal horn, could explain constipation as well.

Orthostatic hypotension

This non-motor complication can appear early in PD but most often has a significant impact on quality of life in more advanced cases. Orthostatic hypotension may be due to multiple factors including sympathetic denervation of the heart, as well as LTS in the sympathetic ganglia, adrenal gland and cardiac tissue.

Tissue Diagnosis

Blood, saliva, and CSF markers are currently being studied but no clear finding has enabled a premotor detection of PD. Proteomics, metabolomics, Total RNA and microRNA levels, as well as gene expression profiles hold hope for a future biomarker.

Numerous tissue biopsies are also being studied. Much of this work is based on the autopsy finding of synuclein deposits in various peripheral tissues. Submandibular gland needle core biopsies, colon biopsies, and skin biopsies have all been published in the past five years. Whether these will allow for a tissue diagnosis of PD, and then premotor PD is unclear.

Conclusion

- 1) Parkinson's disease is a systemic disorder that begins well before the motor findings.
- 2) Genetic testing can identify at-risk cases
- 3) Imaging, fluid, and tissue testing as well as some clinical findings may eventually be used to identify premotor PD

Selected References

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