Biomarkers and Future Treatments for Parkinson's Disease

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Introduction/Objectives

Parkinson's disease (PD) is a disease characterized and primarily diagnosed by its physical manifestations. The symptoms, such as bradykinesia and muscle rigidity, are mediated by loss of dopaminergic neurons in the brain. One major obstacle with PD is that once symptoms are apparent and the disease can be properly diagnosed, the loss of dopaminergic neurons is already severe and any chance for intervention is not possible. Early detection and treatment of PD are the goals of current research for this disease. This review delves into the current state of research into biomarkers for PD as well as possible future treatment targets for the disease and their plausibility.

Background

WHAT IS PARKINSON’S DISEASE?1
- Progressive disease which results in movement disorders due to loss of dopaminergic neurons in the brain
- It is a very slowly progressing disease
- Detection is key to efficacy of treatment
- Visible manifestations of the disease - Clinical (motor) Biomarkers
- Incontinence, Rigidity, Tremors, Drooling, Hypoesthesia

WHAT CAUSES PD?2
- Genetic mutations3,6,8
- SNCA, LRRK2, GBA, MAPT
- Environmental and Non modifiable causes3,8,9,10
- Age**, Head injury, Occupational exposures

PROBLEM OF DETECTION
- Several biomarkers are associated with PD
  - α-synuclein, Laryn Brodsky, Parkinson etc.
- None of identified biomarkers are completely specific to PD
- Testing for biomarkers is expensive or invasive or both
- Other easy to assess biomarkers are highly non-specific i.e dropout or compensation

Conclusions

Parkinson’s Disease is difficult to diagnose early, but some biomarkers may provide some signs for earlier detection. More research is needed on these biomarkers to make them clinically relevant.

Ongoing research may be pointing to a different origin point for Parkinson’s Disease than the central nervous system. This leads to more possible drug targets. There are currently no treatments for Parkinson’s Disease that provide definitive neuroprotection or significantly delay disease progression. Future research into current and future drugs may look at these new drug targets with the hope of neuroprotection and delay of disease progression.

Biomarkers of Parkinson’s Disease

Biomarker: Signs and symptoms present many years before the disease is clinically diagnosable. Biomarkers are of interest due to their potential to be used to guide therapy. Certain biomarkers are more reliable than others.

OLFACTORY LOSS - Many PD patients with loss of sense of smell.
- Loss of smell is normal with aging
- PD patients can have 90% with REMBD confirmed by polysomnography

SUBTLE MOTOR SIGNS - Many PD patients with subtle motor signs
- High variability amongst patients
- No uniform way of measuring motor changes
- Potentially already reached clinically diagnosable PD

Rapid Eye Movement Sleep Disorder - Physically acting out in ones dreams during REM sleep
- Strong evidence as biomarker
- Studies show 80-85% with REMBD confirmed by polysomnography acting PD
- Only one in 4 people with early PD have REMBD
- Time consuming, expensive

Drug Targets

NON-CNS DISEASE PROGRESSION
- Loss of dopaminergic neurons in the substantia nigra pars compacta
- Lead to motor symptoms: bradykinesia, rigidity, and tremor
- Nonmotor symptoms are main part of the prodromal phase
- REM Sleep Behavior Disorder
- Obesity loss
- Hypersomnia
- Comorbidities

POTENTIAL DRUG TARGETS3,4
- α-synuclein protein
  - Conformational length of the GI transit time and this leads to an increase in α-synuclein levels
  - The results in the spreading of this protein from the gut up through the entire nervous system, and then to the brainstem in a prion-like manner
  - Receivers in the GI tract that increase motility and therefore decrease α-synuclein levels16
  - 1. α-synuclein receptor (nicotinic)
  - 2. adenosine receptor (caffeine)
  - Subjects with a history of smoking or caffeine use showed decreased levels of PD

Visual cortex
- CNS controls activity in the GI tract
- Subjects with vagotomy showed a lower incidence of PD
- Could this be the pathway that α-synuclein travels to get to the CNS?

Current Treatments

LEVOSTAT®
- Mechanism: Corrected to dopaminergic via DOPA decarboxylase loss
- Goal validated
- Characterized by “off/del” periods
- Often combined with carbidopa

DOPAMINE AGONISTS6,8
- Mechanism: Stimulates dopamine receptors
- Monotherapy or in combination

Antipsychotics: bromocriptine, ropinirole

COMT INHIBITORS3,17
- Mechanism: Inhibits COMT to increase available dopamine levels
- Levels “on-time” and decreases “off-time”

- Agonist: tolcapone, entacapone

MAO INHIBITORS4,5,6
- Mechanism: Inhibit monoamine oxidase B to increase dopamine levels
- Agonist: rasagiline, selegeline

ANTICHOLINERGICS1,2
- Mechanism: Blocks action of acetylcholine
- Treatment of tremor
- Agonist: benztropine, trihexyphenidyl

ANTI-PARKINSON AGENTS
- Mechanism: Treat to neuronal receptors to treat movement symptoms
- Agonist: benserazide, tramiprosate

Figure 1. Dopamine pathways in the neuron

Figure 2. Prodromal biomarkers of Parkinson’s Disease

Drug Development

• Dopaminergic drugs: dopamine agonists and dopamine reuptake inhibitors are the first-line treatment for PD.
• Non-dopaminergic drugs: anticholinergics, antiseizures, MAO inhibitors, COMT inhibitors are used to treat symptoms and side effects of the disease.
• Neuroprotective agents: these agents aim to slow the progression of PD by preventing or reversing neuronal loss. Examples include riluzole, selegiline, and deprenyl.

Biomarkers of Parkinson’s Disease

- Alpha-synuclein: accumulation of this protein in Lewy bodies is a hallmark of PD.
- Alpha-2 nicotinic receptor: decreased receptor density in PD patients.
- Prion protein: increased expression in PD brain.

- Genetics: Mutations in genes encoding alpha-synuclein, parkin, PINK1, and DJ-1 are associated with PD. These mutations result in the production of abnormal proteins that are toxic to neurons.
- Genes associated with PD risk include SNCA (alpha-synuclein), LRRK2, PARK2, and MAPT (tau). Variants in these genes can increase the risk of PD.

- Vascular factors: Hypertension and diabetes are modifiable risk factors for PD.
- Infections: Certain viral infections, such as HIV, have been associated with an increased risk of PD.

- Environmental factors: Exposure to pesticides, heavy metals, and solvents may increase the risk of PD.

- Smoking: Smoking is a well-established risk factor for PD.
- Obesity: Obesity is associated with an increased risk of PD.

- Nutrition: Poor diet and low intake of certain nutrients, such as vitamin D and B vitamins, may increase the risk of PD.

- Physical activity: Regular exercise may reduce the risk of PD.

- Sleep disturbances: Sleep disturbances, such as sleep apnea, may increase the risk of PD.

- Other factors: Family history, autoimmune diseases, and certain medications have been associated with an increased risk of PD.

- Prognosis: The prognosis for PD varies depending on the severity of the disease and the ability to control symptoms. On average, patients live 10-20 years after diagnosis, but some may live longer or shorter.

- Research: Ongoing research is focused on understanding the underlying mechanisms of PD and developing new treatments to improve outcomes.