Future directions in diagnosis and treatment of Parkinson’s disease

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Objectives

• To get introduced to the new concepts in Parkinson’s disease diagnosis
• To develop understanding of the two main approaches to Parkinson’s disease treatment
• To get introduced to the idea of “referral network for Parkinson’s disease” within the state of North Carolina

Future directions in diagnosis of Parkinson’s disease

Diagnosis of Parkinson’s disease (PD)

“Involuntary tremulous motion, with lessened muscular power, not in action even when supported; with propensity to the trunk forwards pass from a walk to a running pace; senses and intellect being uninjured.”

James Parkinson (1755-1824)
Motor symptoms of PD

- **Tremor** - periodic oscillation of a body part at rest.
- **Rigidity** – increase muscle tone
- **Akinesia (bradykinesia)** - slow movements or paucity of movements
- **Postural instability** – balance/gait problems

Where is the dysfunction in PD?

- Primarily seen in substantia nigra
- Produce dopamine
- PD symptoms become apparent when **60 – 80%** of dopamine neurons are gone in the substantia nigra

### DAT SPECT Scan

Maximal density

Minimal density

**Normal**

**Parkinson’s**

Symptoms preceding the diagnosis of PD

- Loss of smell
- Sleep problems and acting out dreams (REM – sleep behavioral disorder)
- Constipation
- Depression
- Anxiety
- Joint pain and “frozen shoulder” syndrome
- Smaller handwriting
- Softer speech
- Restlessness
- Decrease arm swing (usually on the side of PD)
May be PD starts much earlier than the moment we diagnose it at the doctor’s office?

The answer to this question is the basis for new approaches in diagnosis of PD

**New definition of Parkinson’s disease**

- **Phase I**
  - Preclinical PD
  - No signs or symptoms

- **Phase II**
  - Premotor PD
  - Early non-motor symptoms

- **Phase III**
  - Motor PD
  - Classic motor symptoms

**Symptoms preceding the diagnosis of PD**

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**More so…**

- **Loss of smell** – abnormal in 90% of patients
- **REM – sleep behavioral disorder**
  - 40% of people with just RBD will develop PD in 10 years
  - A combination of RBD, poor smell and color vision increases the chances to develop neurodegenerative disorder in 5 years
  - People with RBD show faster decrease in dopamine level on DAT SPECT scan than normal people
- **Constipation**
  - Biopsy of the colon can reveal alpha – synuclein
Parkinson’s Progression Markers Initiative (PPMI)

- **Description:** observational clinical study to evaluate a cohort of patients and controls
- **Goal:** to identify biomarkers of PD progression
- **Tools:** advanced imaging, biologic sampling and clinical and behavioral assessments
- **Main cohort:** 426 PD diagnosed within 2 yrs and not taking medications and 196 control subjects
- **Additional cohort:** currently recruiting people with poor smell and RBD sleep changes, who do not have first degree relatives with PD
- This study is sponsored by The Michael J. Fox Foundation for Parkinson’s Research.

Parkinson Associated Risk Study (PARS)

- **Description:** observational clinical study to evaluate the risk of development of PD in a cohort of healthy people
- **Goal:** to identify biomarkers of PD progression
- **Tools:** smell test, advanced imaging, biologic sampling and clinical and neurological assessments
- **Main cohort:** over 300 people older than 60 year old with poor or normal smell followed for up to 5 years
- The study is sponsored by Department of Defense and NIH

In summary

- PD starts before motor symptoms are apparent
- The major goal of current research in diagnosis of PD is to establish symptoms and tests (biomarkers) that would be helpful in diagnosing PD before motor symptoms develop
- Several longitudinal studies are currently ongoing to find biomarkers for PD progression
- All of the efforts hopefully will result in new experimental therapeutics that completely prevents PD progression to the motor symptoms originally described by James Parkinson

Future directions in treatment of Parkinson’s disease
Approach to treatment of PD

- Disease management
  - The use of different modalities to help control the symptoms of the disease
  - New approach to targeted health care delivery for PD

- Disease modification
  - The use of different modalities to slow down the symptoms and/or reverse the symptoms

Disease modification: different approaches

- Identification of risk factors for PD
  - to understand how gene-environment interactions trigger the cellular processes that ultimately produce PD

- Neuroprotection / neuromodulation
  - to develop new substances and medications or utilize available on the market medications to protect dopamine-producing neurons

- Replacement of the degenerated neurons
  - Gene therapy
  - Cell transplantation
  - Stem cell transplantation

Disease modification

Today, most scientists believe that both genetic predisposition factors and environmental exposures act together to cause most sporadic cases of PD:

- toxins (MPTP, Rotenone)
- viruses
- oxidative stress
- genes linked to familial PD:
  - alpha-synuclein
  - parkin
  - DJ-1
  - LRRK2
  - UCH-L1
  - PINK1

Disease modification: Trials results of the possible neuroprotective agents to date

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Results</th>
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<tbody>
<tr>
<td>Riluzole</td>
<td>NMDA antagonist</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunophillin</td>
<td>Neurotrophic</td>
<td>Negative</td>
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<td>TCH346</td>
<td>Antipoptotic</td>
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<td>CEP 1347</td>
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<td>Coenzyme Q 10</td>
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<td>Pramipexole</td>
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Possible neuroprotective agents currently in trials

- Pioglitazone
- Isradipine
- Iron chelators
- Green tea polyphenol
- Deep brain stimulation
- Exercise protocols

Approach to treatment of PD

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Comprehensive care in patient with PD

- Pharmacological approach
  - For motor symptoms of PD
  - For non – motor symptoms of PD

- Non – pharmacological approach
  - Physical exercise
  - Physical therapy (gait and balance exercises, falls prevention)
  - Speech therapy (Lee Silverman Voice Therapy)
  - Occupational therapy (help with handwriting, driving, activities of daily living)
  - Music therapy
  - Education about PD

- Deep Brain Stimulation surgery

Q&A: Is there anything I can do for my PD without taking medications?

- Physical exercise
  - Aerobic exercise about 30 min per day, 3 – 4 times per week

- Diet
  - No particular diet modification is known to influence PD

- Vitamin supplements
  - Vitamin E shown to be not effective
  - Other vitamins are not adequately studied at this time
  - About 60% of PD patients are vitamin D deficient, so vit D supplementation is recommended

- Natural products
  - None of them were studied adequately
Q&A: Is Levodopa the best medication to control my symptoms?

- Not necessarily. The choice of the medication depends on your symptoms or type of PD that you have.
- Levodopa is a perfect medication for such symptoms as:
  - Slowness of movements (bradykinesia)
  - Rigidity (tightness of the muscles)
  - Balance and gait issues
- Levodopa is not a very good medication to control tremor.
- Better medications for tremor are:
  - Dopamine Agonists
  - Artane
  - Amantadine

Common motor perils for PD patients and their caregivers

- Motor fluctuations ("on" and "off" phenomena)
- Balance and gait issues
- Tremor

New medications in pipeline for motor symptoms in PD

- New formulation of levodopa
  - Impax (IPX066) and XP 21279 better absorption and prolong action of levodopa.
  - Duodopa (levodopa gel)
  - ND0611 patch (continuous carbidopa solution that can be used with levodopa and allows more levodopa to get to the brain)
- Medications for motor fluctuations
  - Istradefylline – not beneficial
  - Preladenant – in phase III study
  - Amantadine extended release

Q&A: What are the non-motor symptoms of PD?

- While the main symptom of PD is movement problems, there are many other symptoms to be aware of, including
  - sleep disorders
  - constipation
  - sexual dysfunction
  - depression and anxiety
  - cognitive dysfunction
- Without treatment, these symptoms can cause as much discomfort as movement problems and they greatly affect daily routines and quality of life.
Parkinson’s disease: non-motor symptoms

- Depression / anxiety (40 – 65%)
- Dementia (30 – 70%)
- Cognitive impairment: attention, concentration and visuo – spatial orientation
- Psychosis (hallucinations)
- Apathy

Autonomic dysfunction

- REM – behavioral disorder
- Restless legs syndrome
- Excessive daytime

Disruption of sleep

- Olfactory dysfunction
- Taste dysfunction
- Pain (up to 40%)
- Cramps
- Fatigue

Sensory disorders

New medications in pipeline for non-motor symptoms in PD

- Gait and balance
  - Varebicline (Chantix®)
- Impulse control disorders
  - Naltrexone
- Sialorrhea (drooling)
  - Botulinum toxin injections, oxybutynin – clonidine syrup
- Orthostatic hypotension
  - Droxidopa
- Hallucinations and psychosis
  - Pimavanserin

New role of allied health professionals in treatment of PD symptoms

- There is an increase evidence that targeted therapy will have improvement of some dopamine – resistant symptoms
- Physical therapy for gait and balance exercises helps with falls prevention
- Speech therapy with Lee Silverman Voice Therapy has sustained improvement on patient voice for up to 6 months (3 months longer than regular speech therapy)
- The lower – intensity treadmill exercise (50 minutes at 40% - 50% of heart rate reserve 3 times per week) results in the greatest improvement in gait speed, while stretching and resistance exercises improved muscle strength

What PD patients and their caregivers look for in PD care

- Emotional support and empathy
- Knowledge of PD treatment among providers
- Provision of tailored information about PD
- Patient involvement in treatment decisions
- Continuity and collaboration among care providers
- Healthcare accessibility

van der Eijk et al Parkinsonism and Related Disorders 2011;17:360-4.
Building Community Partnerships throughout the North Carolina (ParkNC.org)

New health care delivery for patients with PD

Conclusions

- While the quest for disease-modifying therapies continues, targeted therapies by PD trained specialists bring an improvement for patients with PD.
- There are multiple medications in the pipeline for both motor and non-motor symptoms of PD.
- Aerobic exercise shown to be beneficial for PD in improving the gait speed and overall fitness.
- New approach to targeted health care delivery for PD are in development.

Thank you!