Neurology Update
Movement Disorders
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Parkinson’s Disease
• Neurodegenerative
• Affects 1/100 over 65
• Diagnosed in patients as young as 18

• Categorized as one of the synucleinopathies

Typical Parkinson’s Disease
• Essential Features
  • Rigidity
  • Tremor (resting tremor)
  • Bradykinesia - slowness
  • Walking difficulties

Typical Parkinson’s Disease
• Other Symptoms and Signs
  • Less facial expression
  • Small handwriting
  • Softer speech
  • Swallow trouble
  • Walking difficulties
  • Trouble starting and stopping
  • Shuffling
  • Poor Arm Swing

Typical Parkinson’s Disease
• Other Symptoms and Signs
  • Trouble turning in bed
  • Getting out of a chair
  • Drooling
  • Loss of smell
  • Trouble getting out of a chair
Presentation of Parkinson’s Disease

- **Motor Symptoms**
  - Tremor, bradykinesia, micrographia
- **Non-Motor Symptoms**
  - Loss of smell
  - Constipation
  - Depression/Anxiety
  - Dementia
  - REM Behavioral Disorder

?How does it come on

- Usually starts rather gradually
- Often starts on one side first, then the other

Synucleinopathies

- Parkinson’s Disease
- Dementia with Lewy Bodies
- MSA
- Alzheimer’s with Lewy Bodies

Alpha-Synuclein

- Protein that comes in different forms in the body, found in highest concentration in the brain, but also heart, skeletal muscles and pancreas, skin, lungs, kidney, spleen
- Natural form is approximately 140 amino acid unfolded, abnormal forms are truncated and folded
- Identified in 20 different species
- Unknown functions but plays a role in regulation cell differentiation, synaptic plasticity, management of presynaptic vesicular pool, and dopaminergic regulation
- Present in Substantia Nigra Cells naturally

Alpha-Synuclein

- Abnormal form is where it folds into helical structure, then into insoluble fibrils leading to formation of Lewy Bodies
Misfolded

Alpha-Synuclein

• Research suggests that the disease may start not in the substantia nigra but in the gastrointestinal system and the olfactory bulb
• It's been hypothesized that the alpha-synuclein clumps found in all people with Parkinson's may form in these parts of the body first, before migrating to other parts of the brain.
• Studies show that the spread of folding abnormalities and its damage may spread like a prion disease.
• May lead to new treatment options

Parkinson’s Disease or something else?

• Diffuse Lewy Body Disease
• Medication Induced Parkinson’s
• Multisystem Atrophy (Parkinson’s Plus)
• Progressive Supranuclear Palsy - tauopathy (neuronal loss, neurofibrillary tangles of tau protein)
• Vascular – blood vessel disease, ie Strokes
• Normal Pressure Hydrocephalus
• Head Trauma – rare

Diagnosis

• The Absolute Diagnosis of Parkinson’s Disease or a Parkinson’s Syndrome can be very difficult
• Brain Scan, MRI and CT scans are generally unremarkable in Typical Parkinson’s Disease
• New scan DaTscan now available at higher centers.

Treatment

• Treatment must be individualized for EVERY Patient
• It is not mandatory to start treatment exactly when the diagnosis is established, or to treat every symptom completely

Treatment of Parkinson’s Disease

• Treatment presently is primarily Symptomatic in nature
• Pharmacologic Therapy
• Non Pharmacologic Therapy
• Surgical Therapy
**Medical Therapy**

- **Sinemet**
  - Carbidopa/Levodopa
  - Actually a combination of two medications
  - Carbidopa – prevents the breakdown of Levodopa outside of the brain
  - Levodopa – in the brain converts to Dopamine, directly metabolized from Tyrosine
  - Available at 10/100, 25/100 and 50/200 preparations
  - Average person needs 75 mg of carbidopa daily to prevent decarboxylation
  - Available since 1970
  - Life expectancy of someone with PD before Sinemet was 7 years

**More about Levadopa Therapy**

- Available as both short acting and long acting preparations
- Some patients crush the short acting Sinemet and take dissolved in something to get started in the morning
- Better absorbed on an empty stomach
- Available now in a new form called Rytary

**Dopamine Agonist Medications**

- Bind to the same dopamine receptors as dopamine with agonist effects
- Not as potent as L-Dopa
- Mirapex (pramipexole), Requip (ropinirole), Neupro patch (rotigotine)

**MAO-B Inhibitors**

- Inhibits the natural breakdown of dopamine
- Azilect
- Selegiline
- Eldepryl
- Zelapar

**COMT Inhibitors**

- Entacapone (COMTan)
- Enhance the effects of Levodopa (Sinemet)
- May be helpful for both early and later (fluctuating disease)
- Often times can reduce the dose of Levodopa
- Comes as combination medication with Sinemet, called Stalevo

**Other Medical Therapy**

- Amantadine – actually and antiviral agent that enhances release of stored dopamine in the brain
- More for Tremor, Bradykinesia, and Dyskinesias
- Side Effects: Hallucinations
Medical Therapy

• Anticholinergics
  • Trihexyphenidyl, Benztropine
• More for Tremor and Rigidity
• Side Effects: Dry Mouth, Constipation, Confusion, Hallucinations, Urinary Retention
• Recent data suggest significantly higher risk of developing dementia with long term (3-4 year) use. They include popular antihistamines sold over the counter as sleep aids, such as diphenhydramine (Benadryl, McNeil-PPC Inc), or for allergy relief, such as chlorpheniramine; oxybutynin and tolterodine

Therapeutic Window

Treatment

• Non-pharmacologic
  • Exercise, Exercise, Exercise
• BIG Therapy (LSVT)
• LOUD Therapy (LSVT)
• PWR (Parkinson’s Wellness Recovery)

Managing Parkinson’s

• Dementia
• Depression
  • Usually responds to standard medications
• Psychosis
  • Anti-psychotic agents
• Blood pressure problems – Orthostatic Hypotension

Psychosis

• Antipsychotics
  • Block dopamine

• Atypical Antipsychotics
  • Block serotonin more than dopamine, more selective dopamine blockade

Treatment of Psychosis

Potential Newer treatment
- Nuplazid - (pimavanserin) – up for priority review
- may be the first FDA approved treatment for PDP
- Selective Serotonin inverse agonist targets FHT2A receptors
Surgical Treatment

- Pallidotomy, Thalamotomy
- DBS – Deep Brain Stimulation
  - Indications
    - refractory tremor
    - Too much fluctuation with Levodopa
  - Intestinal dopamine – Duopa

Deep Brain Stimulation

- Subthalamic Nucleus (STN) or Globus Pallidus Internis (GPI)
- Set up controlled electrical field to depolarize nerves and essentially take them out of the circuit.

New Surgical Option - Duopa

- Vitamin E - disproven
- Selegiline - disproven
- Co-enzyme Q10 - disproven
- Azilect - ? – seemingly disproven
- Dopamine Agonists - ? – seemingly disproven
- EXERCISE!! - PROVEN

Future Treatments

- Gene Therapy
  - Genes that convert cells to produce dopamine
  - GNDF (glial cell line-derived neurotrophic factor) – nasal route via nanoparticles – activates survival pathways in dopaminergic neurons
  - Gene introducing GAD (glutamic acid decarboxylase) into ST to increase GABA levels to calm STN activity
  - Gene to replace Amino Acid Decarboxylase
  - Nilotinib – used in Leukemia, recent study effective, increase cellular clearance of alpha-synuclein
  - Stem Cell Therapy

Neuroprotection

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Other Important Issues

- Skin Evaluation is important – Melanoma – risk is up to 2 times normal
- ? Prostate Cancer more common in men – risk may be up to 1.71 times normal
- Care for the Care Giver is critical
  - This is a family journey