AN UPDATE ON NEW TREATMENTS FOR PARKINSON’S DISEASE
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Update of PD treatment research

This presentation will provide an overview on Parkinson’s Disease

• Epidemiology
  • Frequency
  • Risk factors
• Symptoms and signs
  • Motor features
  • Non-motor features
• Treatment
  • Symptomatic treatments
  • Disease modifying therapy
Parkinson’s Disease: how common?

~ 1,000,000 persons with PD in USA

• ~ 3,000 persons in Hawaii
• ~ 300 diagnosed yearly
Parkinson’s Disease

• Annual cost for PD care in the USA is 14.4 billion dollars with total per patient cost of $20,000 per year.
• The cause of Parkinson’s disease is unknown.
• Diagnosis depends on recognition of typical symptoms and clinical features. Currently, there is no diagnostic test.
• There are good medications to treat symptoms but no cure and no way to slow or halt progression of the disease.
PD Diagnosis

- Clinical parkinsonism
  - Bradykinesia – slow movements
  - Rigidity – joint stiffness
  - Rest tremor
  - Postural instability

- Asymmetry of symptoms at onset
- Rest tremor at onset
- Good response to levodopa
- Absence of atypical features
Parkinson’s Disease: Non-motor features

- Impaired olfaction
- Constipation
- Heart rate abnormalities
- Excessive daytime sleepiness
- REM sleep behavior disorder
- Sexual dysfunction
- Fatigue
- Seborrhea
- Dry skin and dry eyes
- Drooling and trouble swallowing
- Bladder dysfunction
- Major depression
- Dementia
- Psychosis
Pre-motor symptoms known to precede onset of the classic motor features

- Impaired Olfaction
- Constipation
Olfactory dysfunction in the Kuakini Honolulu-Asia Aging Study

2,263 men in the study given Brief Smell Identification Test

- Present in 90% of PD patients whether measured by identification, threshold testing or recognition, and occurs early
- Japanese-American men

(Ross et al, Ann Neurol 2006)
The fewer bowel movements reported per day, the greater the risk of developing PD in the future.
Neuropathology:
• Loss of melanin pigment
• Loss of dopamine producing cells in the substantia nigra
• Lewy bodies
• Low striatal dopamine levels
Risk Factors for PD

• Environmental factors associated with increased risk:
  • Environmental toxicants
    • Pesticides
    • Trichloroethylene (TCE)
  • Head injury

• Factors associated with decreased risk:
  • Cigarette smoking
  • Coffee drinking
  • High blood Uric Acid
  • Physical activity
Pesticides and PD Link: Summary

• Evidence indicates that pesticide exposure is associated with higher PD risk

• Specific pesticides implicated include:
  • Paraquat – commonly used herbicide
  • Maneb – commonly used fungicide
  • Rotenone – widely used in home gardening, pest control, fish poison, and commercial insecticide
  • Organochlorines – banned in US over 30 years ago
  • 2,4-D – constituent of agent orange
  • 2,4,5-T – constituent of agent orange

• Recommendations:
  • Avoid these chemicals when possible
  • When contact is necessary, use protective gear
• Kuakini Honolulu-Asia Aging Study: Self report on pesticide exposure (occupation and home exposure) assessed in 1971

• The more years exposure to pesticides, the greater the number of people diagnosed with PD

Cumulative Years of Pesticide Exposure

* number diagnosed with PD per 10,000 people followed for 1 year
Organochlorines and Parkinson’s Disease in the Kuakini Honolulu-Asia Aging Study

- Organochlorines
  - associated with dopaminergic neuron loss in cell culture
  - found more frequently in PD brains
- Organochlorines, including chlordane, heptachlor, and DDT, widely used from 1940s to the mid-1980s to control termites in Hawaii
- Organochlorines used on pineapple plantations until banned in the mid-1980s
- Organochlorines persist in the environment and can be measured in tissue
- HAAS Autopsy Study (705 brains): organochlorines were much more commonly found in brains with Lewy bodies compared to those without
Parkinson’s Disease: Symptomatic Treatment

- **Symptomatic treatment** helps the motor features
  - Carbidopa / levodopa
    - Sinemet©
    - Rytary©
    - Gel infusion (Duopa©)
  - Dopamine agonists including ropinirole, pramipexole, rotigotine
  - Entacapone
  - Amantadine / anticholinergic medications
  - Monoamine oxidase B inhibitors
    - Rasagiline
    - Selegiline
  - Surgical: deep brain stimulation
Levodopa; carbidopa/levodopa; carbidopa/levodopa/entacapone

(Sprenger and Poewe, CNS Drugs, 2013)

- Recommended as first line monotherapy, especially in the elderly

- Advantages
  - Levodopa is the most effective drug for PD motor symptoms

- Disadvantages
  - Short half-life requires frequent dosing
  - High risk for future motor complications
  - Side effects include:
    - Nausea
    - Daytime sleepiness
    - Hallucinations
Dopamine agonists: pramipexole, ropinirole, rotigotine transdermal patch

(Sprenger and Poewe, CNS Drugs, 2013)

• Recommended as first-line therapy for younger patients

• Advantages:
  • May be given 2 or 3 times a day
  • Low potential for causing motor complications such as dyskinesias or wearing off

• Disadvantages:
  • Symptomatic benefit not as great as levodopa
  • Potential side effects include:
    • nausea
    • daytime sleepiness and sleep attacks
    • hallucinations and confusion, especially in the elderly
    • impulse control disorders
Dopamine agonists and impulse control disorders

- Dopamine agonists are linked to impulse control disorders such as:
  - Gambling addiction
  - Hypersexuality
  - Binge eating
  - Excessive spending
  - Excessive computer use

- May occur in as many as 20% of patients on these medications
- The higher the dose, the more likely the disorder
- These behaviors may require dose adjustment.
Parkinson’s Disease: motor fluctuations

• Alterations between periods of good response to levodopa and periods of poor response with severe parkinsonian symptoms
  • Wearing off – medication wears off at end of dose
  • “Off” periods where parkinsonian symptoms occur abruptly and unpredictably
  • Dyskinesias – abnormal involuntary movements caused by excessive levodopa
Continuous levodopa infusion for PD: Duodopa

1. Continuous carbidopa-levodopa solution is pumped into the small intestine
2. Smooths out response to levodopa with more “on” time
3. Significant improvement in activities of daily living
4. Adverse events related to device relatively common but rarely serious
Deep Brain Stimulation (DBS)

(Sprenger and Poewe, CNS Drugs, 2013)

• About 10 to 20% of PD patients are good candidates

• **Best candidates**
  • Levodopa responders
  • Who remain troubled by the motor symptoms despite adequate medication
  • Who are experiencing motor fluctuations and dyskinesias
  • Who don’t have significant memory problems

• DBS does **not** help PD symptoms that are unresponsive to levodopa therapy such as memory problems, speech problems, or balance problems
Deep Brain Stimulation

- DBS requires programming of the stimulator and can take 3 to 6 months to obtain the best results
- Surgical complications include
  - Infection (0-15%)
  - Intracranial bleeding (0-10%)
  - Stroke (0-2%)
  - Lead breakage or movement (0-15%)
PD treatment - disease modifying therapies

- Disease modifying therapies for Parkinson’s Disease – therefore a “cure” require:
  - A way to stop the disease process
  - A way to protect the surviving nerve cells
  - A way to restore or replace the cells that have been lost
Stem cell therapy

• Stem cells are unspecialized cells that can divide and differentiate into many types of specialized cells
Cellular therapy for PD

Multiple cell types may be utilized:

- **Embryonic stem cells (ES)** isolated from human embryos
- **Induced pluripotent stem cells (iPS)** usually from human skin and re-programmed to have the capability to differentiate into multiple cell types
- **Mesenchymal stem cells (MSC)** derived from bone marrow or fat from the patient
- **Neural Progenitor cells (NPC)** derived from fetal or adult neural tissue including ventricular wall and dentate gyrus
Stem cell therapy for PD: current status

- First in-human clinical trial using iPS cell-derived dopamine-producing cells was approved to begin in Japan in August 2018
- Phase I/II to evaluate safety and efficacy
- Subjects must be from Japan
- iPS cells are transplanted into left and right putamen of 7 subjects
- Subjects will take immunosuppressant to avoid transplant rejection
- Future trials to take place in North America
Exercise and PD

• Exercise might lower the risk of developing PD or improve function and delay progression
• Observational studies in humans generally indicate that more physical activity is associated with lower PD risk, although results have not been definitive
Types of Exercise

• Flexibility training
  • Stretching
  • Yoga
  • Tai chi

• Tai chi trial (*Li et al, NEJM 2012*)
  • 195 PD subjects randomized to tai chi, resistance training, or stretching
  • Tai chi associated with significantly greater improvement in balance and fewer falls
  • Findings persisted 3 months after intervention
Types of Exercise

• Aerobic exercise
  • walking, swimming associated with improved motor action, balance, and gait in patients with PD
  • evidence lacking regarding whether aerobic exercise may slow progression
    (*PLOS one, 2014*)

• “Forced” exercise
  • improved dopamine levels and motor function in rodent PD model
  • Associated with 35% improvement in Unified PD Rating Scale motor scores in those randomized to forced exercise compared to those on self-paced exercise in one small trial of 10 subjects
    (*Ridgel et al, Neurorehabil Neural Repair 2009*)
Types of Exercise

• Dance and PD
  • Dance (foxtrot, tango, Irish dancing) significantly improved UPDRS motor scores, balance and gait speed when compared to no intervention
  • When compared with other exercise interventions, significant improvements found in balance
  • Long term effects unknown
Exercise and PD

• Skill training with exercise more effective than regular exercise in animal models of PD

• Skill training may lead to enhancement of nerve connections
Mediterranean Diet and Parkinson’s Disease

• Mediterranean diet characterized by:
  • High intake of vegetables, beans, fruits, and grains
  • High intake of polyunsaturated fatty acids – olive oil, vegetable oil
  • Moderately high intake of fish
  • Low to moderate intake of dairy products and meat
  • Regular consumption of wine with meals
Mediterranean Diet and Parkinson’s Disease

• Recent study comparing PD subjects to non-PD control subjects found:
  • PD subjects were less likely to adhere to Mediterranean diet
  • Among PD subjects, greater adherence to Mediterranean diet was associated with later age of PD onset
Mediterranean Diet and Parkinson’s Disease

• Possible reasons for beneficial effects of Mediterranean diet on PD:
  • Fruits and vegetables are rich sources of antioxidants
  • Vegetables such as tomatoes, potatoes, and peppers contain nicotine that is associated with reduced risk of PD
  • Milk has been associated with higher risk of PD
  • Polyunsaturated fatty acids associated with decreased PD risk
Resources

– Hawaii Parkinson Association: www.parkinsonshawaii.org
– Fox Foundation: www.michaeljfox.org
– National Parkinson Foundation: www.parkinson.org
– Parkinson’s Disease Foundation: www.pdf.org
– The Science of Parkinson’s disease: https://scienceofparkinsons.com/about/
– Information on clinical trials: Clinicaltrials.gov