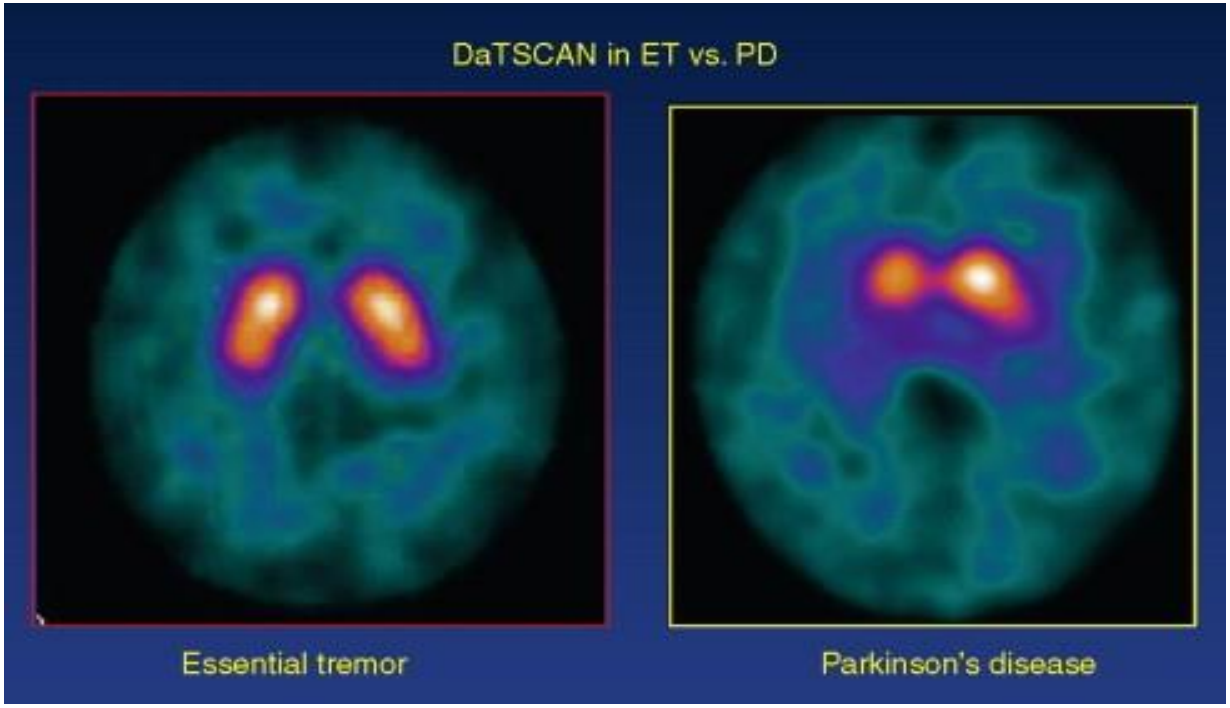
Precision Medicine to Identify Optimal Diagnostic and Therapeutic Interventions for Parkinson's Disease (PD)



Disclosures

- The authors have no financial conflicts of interest to report.
- Instrumentation with accelerometers is not approved for human use by the Food and Drug Administration.

Introduction

- Parkinson's disease, the second most common neurodegenerative disorder afflicting 10 million people worldwide (de Lau and Breteler, 2006) and the fourteenth leading cause of death in the United States, is caused by the death of dopaminergic neurons that regulate movement in the substantia nigra pars compacta (National Parkinson Foundation, 2021).

- L.M.L. de Lau, M.M.B. Breteler, Epidemiology of Parkinson's dsease, Lancet Neurol. 5 (2006) 525–535.
- National Parkinson Foundation, What is Parkinson's? Retrieved from, (2021) . http://www.parkinson.org/parkinson-s-disease/pd-101/what-is-parkinson-s-disease

Introduction

- Mechanisms contributing to the development of Parkinson's disease in vulnerable individuals
  - Protein misfolding
  - Protein aggregation
  - Mitochondrial dysfunction

Introduction

- In about 25 percent of patients, clinicians incorrectly diagnose Parkinson's disease.
- Causes of misdiagnosis include a lack of algorithms and inadequate use of diagnostic modalities.
- We have developed algorithms for diagnosis and treatment based on the review of available knowledge.

Methods

- We reviewed the key literature on the pathogenesis of Parkinson's disease on PubMed and Google Scholar in order to propose guidelines for the development of diagnostic and therapeutic interventions for people with Parkinson's disease and related conditions.

Results

- Different diagnostic modalities (structured interview and examination, laboratory assessments, neuropathology, genetic testing, neuroimaging) will form the basis for our algorithm for the diagnosis and treatment of Parkinson's disease and related conditions.

Pathogenesis

- a) Alpha-synuclein protein misfolding
  - Misfolding of alpha-synuclein, a normal cerebral protein, occurs in PD.
  - Protein folding and refolding of the misfolded proteins occurs via a group of molecules known as chaperones and co-chaperones such as Hsp70 and Hsp 90 and their Co Chaperone Hsp 40.

Pathogenesis

- b) Dysfunctional ubiquitin-proteasome system
  - Proteosomes are organelles responsible for protein turnover.
  - Diminished activity of these organelles may result in abnormal protein accumulation in the basal ganglia and cause damage which may contribute to the development of Parkinson's disease.

Pathogenesis

- c) Mitochondrial dysfunction
  - Mitochondrial dysfunction has been found in many cases of idiopathic or hereditary Parkinson's disease.
  - The neurotoxic alpha-synuclein in its oligomeric form can interact with a mitochondrial receptor resulting in increased oxidative damage due to reduced mitochondrial respiration.

Diagnostic Modalities

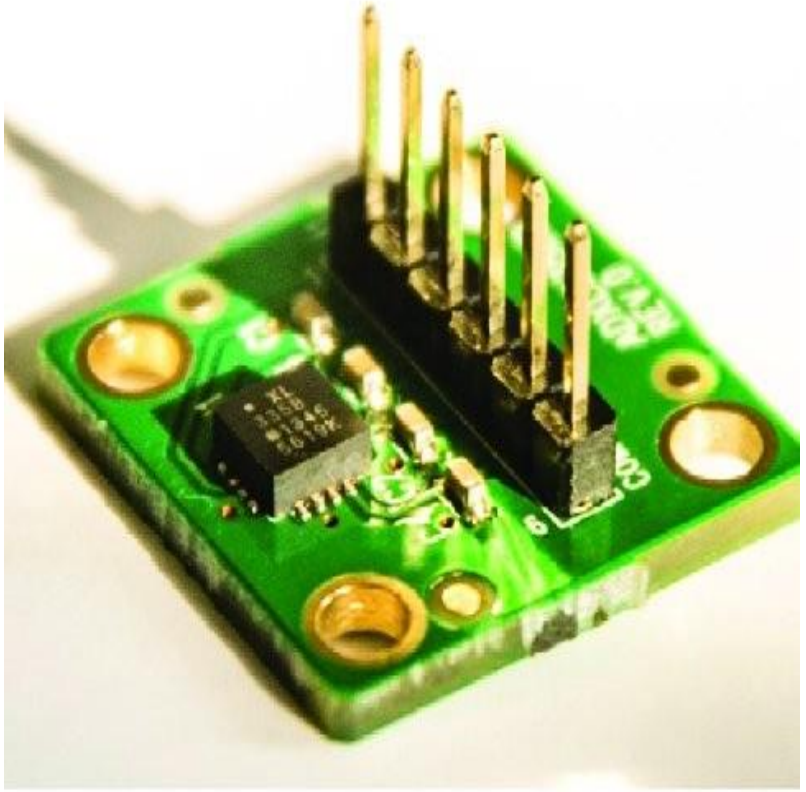
A) Tri-Axial Accelerometer:

Low-cost accelerometers are attached to the upper and lower limbs to generate a continuous three diminutions representation of the movements.

Patients and controls were assessed through a test-retest method.

The degree of tremors is rated clinically by trained examiners

The output of the accelerometers can be interpreted using Fast Fourier Transforms and Continuous Wavelet transforms by experts for diagnosis and therapy.



McKay GN, Harrigan TP, Brasic JR. Alow-cost quantitative continuous measurement of movements in the extremities of people with Parkinson's disease. MethodsX 2019; 6:169-189. PMID: 30733930 https:// doi.org/10.1016/j.mex.2018.12.017

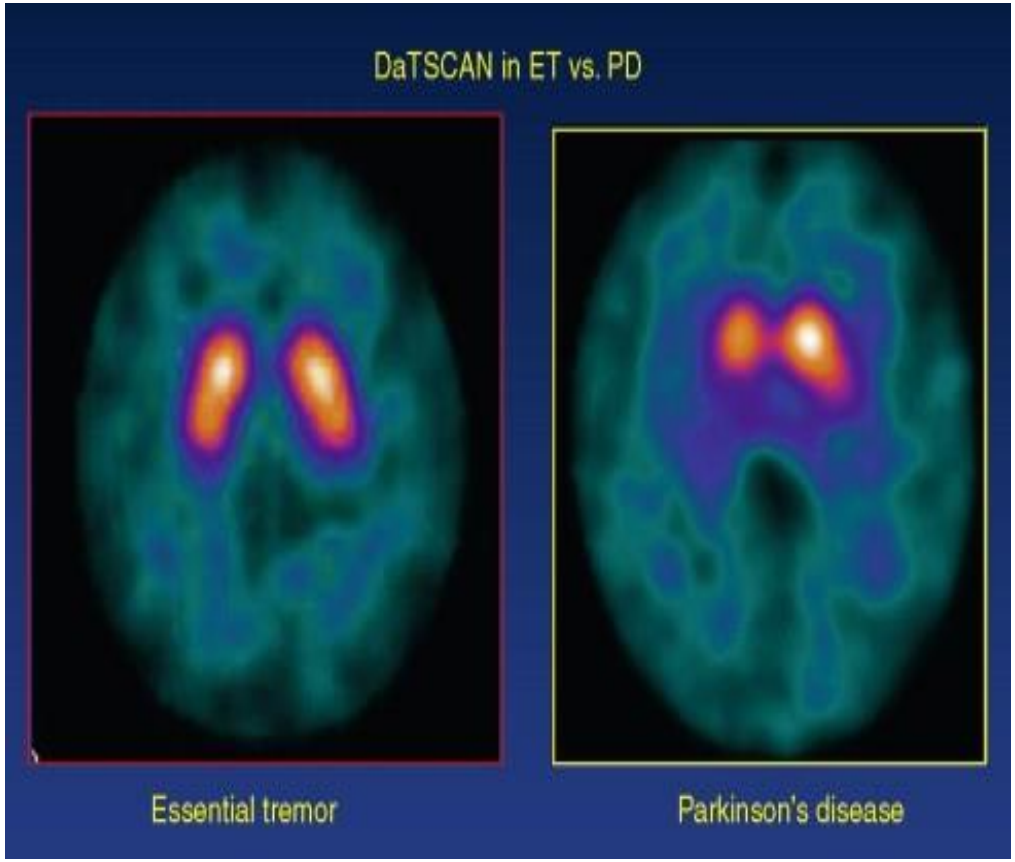
Diagnostic Modalities:

B) Dopamine Transporter Single-Photon Emission Computed Tomography (DAT-SPECT):

SPECT is a method of molecular imaging in which a gamma ray-emitting radioactive isotope is tagged to a molecule of interest. In patients with Parkinson's disease, labeled cocaine derivatives such as Ioflupane for DAT-SPECT is most widely used.

Highly Sensitive and Specific.

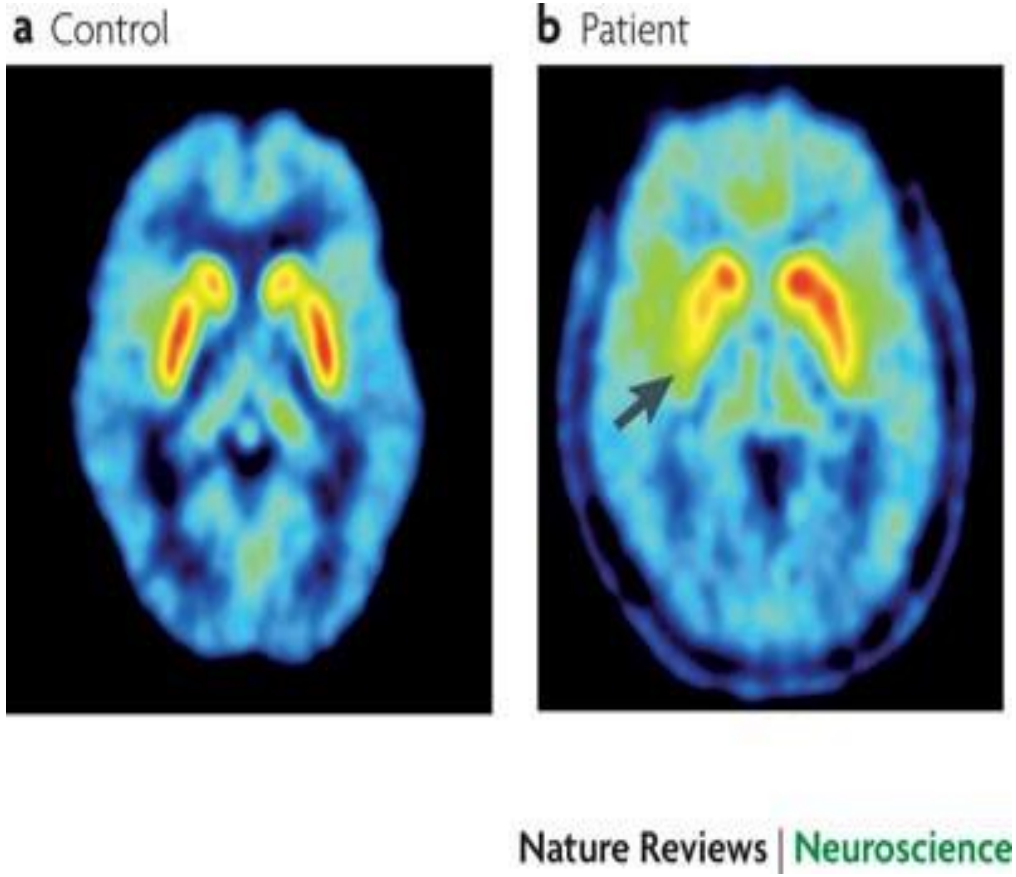
A major disadvantage of SPECT, when compared to other methods of nuclear imaging such as PET, include the limited resolution of images for the visualization of basal ganglia in PD.



Diagnostic Modalities:

C) Positron Emission Tomography (PET):

PET is another method of molecular imaging in which a positron-emitting radioactive isotope is tagged to a molecule of interest. Fluorine is injected intravenously into patients with Parkinson's disease. Fluorine can be attached to either DOPA or deoxyglucose. Flurodopa F18 is taken by the presynaptic neurons in the basal ganglia particularly the caudate and putamen



Diagnostic Modalities:

- **d) Genetic and Molecular Testing :**
- **1 Reverse Transcription Polymerase Chain Reaction (RT-PCR)**
  - Detect genetic mutations in hereditary cases
- **2) Protein Misfolding Cyclic Amplification**
  - Detects misfolded alpha-synuclein protein with high sensitivity and specificity
- **3) Ubiquitination assay for ligase enzyme**
  - Detects parkin gene mutations in autosomal recessive cases
  - Detects the activity of the parkin ubiquitin ligase enzyme which is important for protein turnover.

Diagnostic Modalities:

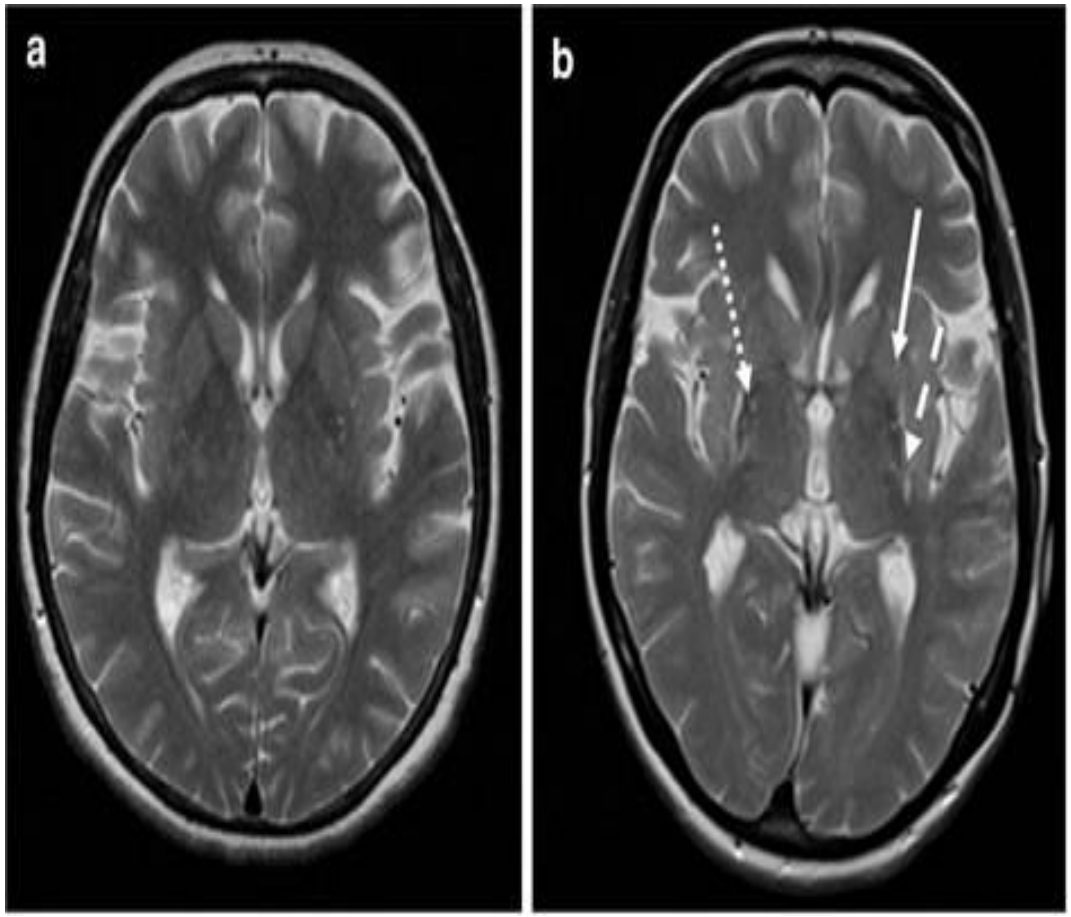
E) Other Modalities:

Used if PD is associated with another neurological condition such as epilepsy or stroke.

1)Transcranial Sonography

2) Computed Tomography(CT)

3) Magnetic Resonance Imaging (MRI)



Algorithm for Diagnosis of Parkinson's Disease (ADPD)

- **Step 1:**
- Obtain a family history of PD and or other movement disorders
- History of Present Illness:
- Confirm the presence of bradykinesia with/without static tremors and or rigidity.
- Rule out Parkinsonism
  - a) Progressive supranuclear palsy (PSP) which is characterized by gaze palsy
  - b) Shy-Drager syndrome which is characterized by autonomic dysfunction
  - c) Cortical base degeneration which is characterized by early cortical signs as speech deficits and cognitive decline
- Rule out traumatic brain injury (TBI)

- **Step 2:**
- Clinical examination:
- Inspection: Static regular tremors like pill rolling
- Tone: Rigidity of upper and or lower extremities
- Gait: Bradykinesia and characteristic shuffling gait

Algorithm for Diagnosis of Parkinson's Disease (ADPD)

- **Step 3:**
- Obtain permission to investigate the use of mechanical accelerometer
  - Simple and cheap method
  - Accurate grading of tremors.
- The Food and Drug Administration (FDA) does not yet approve the general use of this procedure on humans.

McKay GN, Harrigan TP, Brasic JR. Alow-cost quantitative continuous measurement of movements in the extremities of people with Parkinson's disease. MethodsX 2019; 6:169-189. PMID: 30733930 https://doi.org/10.1016/j.mex.2018.12.017 Step 4:

- a) With a family history PD
- Genetic and molecular testing
-
- b) Without fFamily history of PD
  - 1): Without other condition
    - DAT SPECT
    - Reliable and widely available imaging modality
  - 2) With another condition (epilepsy or stroke)
    - Transcranial Sonography
    - CT
    - MR

Treatment

- **Standard medications**
  - a) L-DOPA/carbidopa
    - L-DOPA
      - Potent
      - First line of treatment in the early stages
      - Decarboxylated in the body to dopamine
    - Carbidopa
      - Prevents decarboxylation outside the brain
      - Reduces adverse effects
  - b)Dopamine agonists
    - Pramipexole
      - Stimulate the dopaminergic receptors in the basal ganglia

Treatment

- c) Catechol-O-methyl-transferase (COMT) inhibitor
  - Tolcapone
  - Entacapone
  - Inhibit the enzyme catechol methyl-transferase
  - Increase dopamine availability in the basal ganglia
- d) Monoamine oxidase inhibitors
- Selegiline
  - Inhibit MAO
  - Increase the availability of dopamine in the basal ganglia

Treatment

- **Experimental drugs**
  - Carbenoxolone
    - Enhances the activity of Hsp 90 in rat models
    - Reduction of misfolded alpha-synuclein protein in neurons
    - Improves motor functions
  - Coenzyme Q10 (Ubiquinol-10)
    - Co-factor for complexes 1, 2, and 3 for the electron transport chain in the mitochondria
    - Might be helpful in patients taking L-DOPA with wear-off symptoms

Treamtent

- **Experimental drugs**
  - Immune therapy
    - Granulocyte-macrophage colony-stimulating factor (GM-CSF) (sargramostim)
      - Cytokine produced by T- regulatory cells
      - Protects against basal ganglia degeneration

Treatment

Surgical methods

a) Deep brain stimulation

- Inhibits signals from the basal ganglia
- Marked improvement in many patients

b) Thalamotomy

- Destruction of thalamus
- Benefit for tremors

Treatment

- **Surgical Methods**
  - c) Pallidotomy
    - Destruction of globus pallidum
    - Benefits
      - Tremors
      - Bradykinesia
      - Levodopa-induced dyskinesias
  - d) Subthalamotomy
    - Destruction of the subthalamic nucleus
    - Benefits
      - Tremors
      - Rigidity
      - Bradykinesia
      - Levodopa-induced dyskinesias

Algorithm for Treatment of Parkinson's Disease (ATPD)

- **Step 1:**
  - Exercise
  - Rehabilitation medicine
  - L-DOPA/carbidopa
- **Step 2 to obtain resolution of symptoms and signs:**
  - Exercise
  - Rehabilitation medicine
  - Escalate L-DOPA/carbidopa dose until limited by adverse effects

Algorithm for Treatment of Parkinson's Disease (ATPD)

- **Step 3:**
  - Exercise
  - Rehabilitation medicine
  - L-DOPA/carbidopa
  - Consider MAO-B inhibitor
  - Consider COMT inhibitor
  - Consider co-enzyme (Ubiquinol-10)
- **Step 4:**
  - Consider deep brain stimulation

Our Algorithm for Treatment

- **Step 5:**
- Consider surgical methods (radiofrequency or radiosurgery procedures)
  - Pallidotomy
  - Thalamotomy
  - Subthalamotomy
- **Step 6:**
- Consider potential new treatments
  - Immunotherapy
  - Gene therapy
  - Cell transplantation

Conclusion

- Clinicians, administrators, policy planners, advocates, and other concerned individuals will benefit from the adoption of our algorithms for the diagnosis and treatment of Parkinson’s disease.

Questions?

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