Movement Disorders Update
Ian Bledsoe, MD, MS
Caroline Tanner, MD, PHD

Disclosures

Ian Bledsoe, MD, MS
• Compensation for serving on Advisory Board: Biogen
• Personal fees for consulting: Boston Scientific, Bagatto Inc., LEK Consulting, Amneal Pharmaceuticals

Caroline Tanner, MD, PHD
• An employee of the San Francisco Veterans Affairs Medical Center and the University of California – San Francisco.
• Receives grants: the Michael J. Fox Foundation, the Parkinson’s Disease Foundation, the Department of Defense, BioElectron, Roche/Genentech, Biogen and the National Institutes of Health,
• Compensation for serving on Data Monitoring Committees: Voyager Therapeutics, Intec, Northwestern University
• Compensation for serving on Steering Committee: Partners, Biogen
• Personal fees for consulting: Neurocrine Biosciences, Adamas Therapeutics, Acorda
Part 1:
2 cases
DBS trial overview

Case 1 - background

- Normal cognitive and motor milestones
- Mild learning difficulties elementary school
- Normal motor function – competed in sports
- No neurologic FH

Mother: Puerto Rican/Mexican
Father: Mexican
**Age 15**
- Falls

**Age 18**
- Neurologist eval
- Exam:
  - Dysarthria
  - Impaired tandem

  MR Brain: Read WNL

**Age 19**
- Saccadic pursuit
- Dystonic posturing right hand
- Ankle clonus
- Wide-based gait

  Invitae Hereditary Dystonia Panel negative

**Age 20**
- More falls
- Wide-based gait
- Unable to tandem
- “No cerebellar signs”

  Chromosome analysis, microarray WNL

**Age 21**
- Wheelchair
- Slurred speech
- Worsened cognitive decline

  Whole Exome Sequencing: unrevealing

  No improvement with levodopa
Video

Exam summary

- MOCA 10/30 (normal 26+)
- Severe dysarthria
- CN: impaired supraduction
- Generalized dystonia – face, neck, trunk, arms, legs
- Mild distal weakness: IO BL, FPL on left
- Mild spasticity throughout; hyperreflexic; clonus
- UE dysmetria
- Severe gait ataxia. Falls instantly with narrow stance
### Interpretive Results Table

<table>
<thead>
<tr>
<th>Gene/Test</th>
<th>Technical Result</th>
<th>Variant Type</th>
<th>Inheritance</th>
<th>Clinical Relevance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATXN10</td>
<td>1911 and 12 repeats</td>
<td>Repeat Expansion</td>
<td>Autosomal Dominant</td>
<td>Pathogenic</td>
<td>Normal (&lt;=22), Borderline (23-899), Positive (&gt;=700)</td>
</tr>
<tr>
<td>ATXN3</td>
<td>82 and 29 repeats</td>
<td>Repeat Expansion</td>
<td>Autosomal Dominant</td>
<td>Pathogenic</td>
<td>Normal (&lt;=40), Borderline (41-52), Positive (&gt;=83)</td>
</tr>
</tbody>
</table>

- Primarily Mexican and Brazilian cohorts
- Ataxia +/- seizures, hyporeflexia
- Rare descriptions of combined SCA10 & SCA2

**SCA 3**
Machado-Joseph Disease

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Baizabal-Carvallo et al, 2015
Repeat expansion disorders

- Huntington disease (HTT)
- SCA 1, 2, 3, 6, 7, 8, 10, 12, 17
- Spinobulbar muscular atrophy (AR)
- Fragile X-associated tremor/ataxia syndrome (FMR1)
- Friedreich ataxia (FXN)
- Huntington disease-like 2 (JPH3)
- Myotonic dystrophy type 1 (DMPK)
- DRPLA (ATN1)
2 main points

- WES misses trinucleotide and other repeat expansion disorders
- SCA's may be highly heterogeneous

Case 2 - 46 yo woman with left side weakness, abnormal movements

- Normal motor milestones as child
- Age 3 - motor difficulty in right foot
- Involuntary right plantar flexion/ankle inversion & falls (unclear if coexisting weakness)
- After 2 years, completely resolved spontaneously
Late 20’s

- New abnormal posturing and difficulty with motor control on left
- Declining fine motor control/dexterity left hand
- Unwanted posturing left arm and leg
- Tightness left shoulder/arm
- Unwanted elbow/wrist flexion, plantar flexion, ankle inversion, toe flexion
- Mild dysphagia, slurred speech
- Impaired balance, occasional falls

Headaches, worse with coughing/sneezing

2000: MRI brain/MR cervical spine

Chiari I malformation
- Cerebellar tonsils descended to level of posterior arch of C1
- Small syrinx at level of dens

Stable on serial imaging; declined surgical decompression
30’s – 40’s

- New speech difficulty
- Tight/strangulated quality
- Throat tightness
- New posturing in right hand when writing and in right leg with movement
- No neuroleptic exposure
- Prior levodopa trial without benefit

- No FH of neurologic disease or movement disorder
Age 46

• MOCA 27/30

• Cervical dystonia – left tilt, BL trapezius hypertrophy

• No definite dysmetria

• CN:
  rotatory nystagmus on rightward gaze
  Mild left facial weakness (spares forehead)
  mild tongue weakness

• Distal > proximal weakness L arm and leg (FE/IO, dorsiflexion)

• MSR: 2+, symmetric LE's; slightly brisker UE's.
  No hoffman's. Plantar response flexor BL. No ankle clonus

• Video clip
Pathogenic variant in ATP1A3

- c.1838C>T (p.Thr613Met)
  - Most common variant reported in rapid-onset dystonia-parkinsonism (RDP) – DYT12

- AD inheritance with incomplete penetrance

- \textit{de novo} occurrence common

- ATP1A3 encodes for \(\alpha3\) subunit of Na+/K+-ATPase

Brashear, 2007; Brashear, 2018
- ATP1A3-related neurologic disorders
  - Clinical continuum
  - At least 3 distinct phenotypes:
    - Rapid onset dystonia-parkinsonism (RDP)
    - Alternating hemiplegia of childhood (AHC)
    - Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS)

Brashear, 2018

- ATP1A3-related neurologic disorders
  - Some affected individuals with intermediate phenotypes
    - Only a few features
    - Do not fit well into any of the 3 major phenotypes
Characteristic RDP

- Abrupt onset dystonia with parkinsonism (days to weeks)
- Absent/minimal L-dopa response
- Bradykinesia & postural instability
- Not typically rest tremor
- Often fever, physiologic stress, alcohol trigger Sx onset
- After initial appearance Sx's stabilize with little improvement
- 2nd episode can occur with abrupt Sx worsening

- Typically strong rostrocaudal gradient of symptoms (regional, not temporal)
  - Face > arm > leg
- Age of onset usually 4 – 55 years
- Onset between 9 & 14 mos or after age 60 has been reported
• This pt with some atypical features for RDP
  - No abrupt onset
  - Rostrocaudal gradient not clearly present

• Botulinum toxin injections in left arm/leg with some benefit

Main Thoughts

• Benefit of next generation sequencing, panel testing
  - Particularly with complexity/unpredictability of some phenotypes

• But…. subtleties of exam / clinical phenotyping remain indispensable in guiding testing

• Constant re-evaluation of signal vs noise
Brief update in DBS trials

- Using neurophysiology to target adaptive deep brain stimulation for movement disorders
- Starr Lab / Movement Disorder & Neuromodulation Center

Conventional Deep Brain Stimulation (DBS)

DYT1 dystonia pre-DBS s/p BL GPi DBS
Conventional Deep Brain Stimulation (DBS) - challenges

STN DBS stim-induced dyskinesia

Adaptive DBS

Tinkhauser, et al. 2017
Oscillatory activity correlates with specific motor signs

Prototyping adaptive DBS in clinic

UCSF study – Brain sensing and adaptive DBS in movement disorders

- 7 PD, 1 dystonia
  - RC+S: ipsilateral basal ganglia & cortical leads

- Ongoing sensing at home x 6mos
  - Identify personalized physiologic signatures of specific motor states

→ adaptive DBS

- Intensive data streaming at home x 1mo before stim
Example contact locations patient 1

STN lead location

Cortical lead location

TRACKING MOTOR STATES
The Economic Burden of PD 2017 - 2037

Excess Medical Costs Due to PD, 2017: $25,348 Billion

<table>
<thead>
<tr>
<th>Age</th>
<th>Cost in Billions</th>
<th>Percentage of Total</th>
<th>Excess Cost Due to PD ($ Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-75</td>
<td>4,353</td>
<td>18%</td>
<td>17,318</td>
</tr>
<tr>
<td>85+</td>
<td>11,047</td>
<td>45%</td>
<td>29,354</td>
</tr>
<tr>
<td>Overall</td>
<td>15,498</td>
<td>100%</td>
<td>51.9 Billion</td>
</tr>
</tbody>
</table>

Indirect Costs Due to PD, 2017: $26,509 Billion

Total Economic Burden Of PD, 2017: $51.9 Billion

Projected Increase in Total Economic Burden 2017-2037

<table>
<thead>
<tr>
<th>Year</th>
<th>2017</th>
<th>2027</th>
<th>2037</th>
</tr>
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<tbody>
<tr>
<td>$ in Billions</td>
<td>51.98</td>
<td>67.18</td>
<td>79.18</td>
</tr>
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</table>

Tanner et al, presented at IPMDS 2019

Parkinson’s Disease Treatment Public Health Perspective

1ary Prevention

3ary Prevention

2ary Prevention

HEALTH

PRECLINICAL

PRODROMAL PD

PARKINSON’S DISEASE
Primary Prevention:

GOAL: Prevent pathogenesis; preserve health

Approaches:

Avoid causative factors
Encourage protective factors

Some Factors Associated with a Higher Risk of Parkinson’s Disease

- Pesticides
- Polychlorinated Biphenyls
- Head Injury
- Solvents
- Age
- Metals?
- Air Pollution
- Male Gender
### Veterans: PD & Service Related Disability

- **Agent Orange:** Vietnam veterans may be eligible
- **Service at Marine Base Camp Lejeune:** Water contaminated with solvents PERC & TCE; May be eligible if 30 or more days of service 8/1/1953 to 12/31/1987
- **Traumatic Brain Injury:** May be eligible for secondary service connection for PD, AD, FTD, DLB, if manifest within 15 years of moderate or severe TBI.

[https://www.publichealth.va.gov/exposures/health-concerns.asp](https://www.publichealth.va.gov/exposures/health-concerns.asp)

### Secondary Prevention

**Prodromal phase:**
- Difficult to identify
- Most features non-specific
- More specific features are:
  - Rare (RBD) &/or
  - Costly (PSG, DaTScan)

→ **No feature predicts PD 100%**
Secondary prevention – Prodromal PD

Video

Study Goal: Longitudinally assess cohort of unaffected individuals at high-risk of developing motor features of PD within 2-4 years due to evidence of dopaminergic deficit

Intensive in-clinic assessment N=~400

At-risk participants assessed with DatScan

Remote risk screening: UPSIT, genetic risk score, digital sensor technologies

Leverage scalable risk-screening platforms, such as FI

Generalizable risk-assessment using PROs (e.g., FmHx, constipation, etc.)

Existing cohorts at-risk due to RBD or rare genetic mutations

Additional remote assessments allows for in-clinic resources to be prioritized

Likely to include international partnerships

Primary Objective: Establish feasibility of identifying cohort; identify clinical, imaging, and biologic outcomes of disease progression in prodromal PD to be used in future ‘prevention’ trials

Secondary Objective: Improved understanding of natural history of prodromal PD

Participants at-risk for PD who also demonstrate evidence of dopaminergic deficit considered highest risk for developing motor features (PARS study)

PPMI 2.0 – PRODROMAL: OBJECTIVES
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PPMI 2.0 – PRODROMAL: OBJECTIVES

Enrolling 2020

Some Factors Associated with a Lower Risk of Parkinson’s Disease: Clues for Preventative Therapies?

- Physical activity
- Tobacco Use/Exposure
- Coffee & Tea Drinking
- Flavonoids?
- PUFAs?
- Higher serum urate
- Ca channel blockers
- Statins?
- Higher Vitamin D
- Female gender; Estrogens?
Preventing Disease Progression

Recent Trials with Negative Results:

**SURE PD**: Inosine $\rightarrow$ Urate elevation (PSG, NIH, Phase III)

**STEADY PD**: Isradapine $\rightarrow$ CA channel blocker (PSG, NIH, Phase III)

**NIC PD**: Nicotine patch (PSG, MJFF/IPF Germany, Phase II)

### Preventing Disease Progression

**Repurposing CML Drug Nilotinib**

**Mechanism**: c-Abl Inhibition

Two Phase II trials: placebo (PB), 150 mg, 300 mg

**GEORGETOWN U**: Single Center, RDB, 75 pts. on l-dopa; 12 months Nilotinib

Results – Published 12/2019:
- PD symptoms improved in 150 mg, worsened at 300 mg
- SAE’s: 17% PB, 27% 150 mg, 57% 300 mg
- Falls: 39% PB, 54% 150 mg, 61% 300 mg
- Nilotinib small amounts in CSF in 150 mg & 300 mg

Conclusion: Meets primary end points of safety, tolerability and presence in CSF; **Phase III study indicated**

**NILO-PD**: Multicenter, RDB, 25 PSG sites, 75 pts. On l-dopa; 6 months Nilotinib

Results – Not published - Press release 12/6/2019; Results 2/2020 at PAS-MDS
- Failed to meet primary end point for efficacy, biomarkers of effect
- Safe and tolerable

Conclusion: **Phase III study NOT indicated**
In Progress: Immunotherapeutic Approach in PD - Anti Alpha-Synuclein

Trials In progress (Not Recruiting):
- PASADENA
- SPARK

GOAL: Promote the clearance of misfolded alpha-synuclein targeting the underlying disease mechanism to slow or halt progression.

STUDY DRUG: Monoclonal Antibody Infusion against alpha-synuclein - blocks cell to cell transmission by blocking uptake of misfolded endogenous alpha synuclein

Roche – PRX002

A Phase 2 Study of Anti-α-Synuclein Antibody in Early Parkinson’s Disease

- PRX002 is an INFUSION of a humanized monoclonal antibody against an epitope on the C-terminus of human α-synuclein
- Aggregated and phosphorylated α-synuclein is the major component of pathological hallmark lesions in PD
- Antibody has a high affinity for pathologic forms of α-synuclein consisting of oligomers and fibrils, ultimately preventing propagation and neuronal cell death
- Early PD: (within 2 years from dx, H&Y <= 2, MAO-I-treated only, not anticipated to start a new dopaminergic rx for 1 year)

RESULTS COMING → 2020
- New PHASE III Trials: Early PD, Levodopa Treated PD → 3rd Quarter 2020
Biogen – BIIB054
A Phase 2a Study of the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson’s Disease

- **BIIB054** is an *INFUSION* of a humanized monoclonal antibody against an epitope on the **N-terminus** of human α-synuclein

- Antibody has a high affinity for aggregated pathological forms of α-synuclein as well, to ultimately prevent propagation and neuronal cell death

- **Adopted by the Parkinson’s Study Group**

- Early PD (within 3 years from dx, H&Y <= 2.5, UNTREATED for at least 12 weeks and not anticipated to start a dopaminergic rx for 6 months)

- **May proceed with Phase III pending results**

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**SPARX3: High Intensity Exercise**

**Goal:** Assess efficacy of progressive high-intensity endurance exercise as first-line therapy for PD

**370 Participants with Early PD (not yet started DA therapy)**

*Expect to enroll 5-10 at UCSF*

**Enrolling ~ April/May 2020**
**Hypothesis:** Sensor measurements may provide a more rapid and precise assessment of drug effect, which may substantially accelerate development of putative disease modifying drugs.

- 12 month device study
- Early untreated PD
- At home & In clinic assessments

**Tertiary Prevention**

**Goal:**

Improve quality of life in people with PD by:

- Reducing disability,
- Limiting or delaying complications
- Restoring function
Levodopa

- Most effective and widely used treatment in PD
- Dopa decarboxylase (carbidopa) inhibits peripheral LD metabolism—more levodopa CNS availability (improves tolerability reducing nausea)
- Early PD simple dosing schedules, becomes more complex in advanced PD
- Short half-life (1.5 hours)
- As PD progresses, conversion of LD to dopamine, storage, release, becomes unpredictable
- Intermittent/pulsatile release of dopamine in the striatum, produces changes in the postsynaptic receptors leading to motor complications and dyskinesia (70% after 5 years)

Reducing Disability: Motor Fluctuations & Dyskinesias

Adapted from Hauser RA. Geriatrics. 2006;61:14-20.
### Motor Fluctuations with L-dopa Induced Dyskinesias (LID)

- Video

### Recently Approved Drugs for PD OFF & Levodopa Induced Dyskinesias

2017:

**Safinamide/Xadago™:**
- Mechanism: MAOB Inhibitor;
- Indication: Adjunct to L-dopa for OFF episodes

**Amantadine Extended Release/Gocovri™:**
- Mechanism: NMDA receptor antagonist
- Indication: Dyskinesias in patients with PD receiving L-dopa, w/ or w/o concomitant DA medications
Recently Approved Drugs for PD OFF

2018:

**Levodopa inhalation powder/Inbrija™**

**Mechanism:** Pulmonary absorption bypasses GI tract; onset within 10 minutes

**Indication:** Intermittent treatment of OFF episodes in patients with PD treated with carbidopa\levodopa

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Recently Approved Drugs for PD OFF

2019:

**Istradefylline/Nourianz™**

**Mechanism:** Adenosine Receptor Antagonist

**Indication:** Adjunctive treatment to levodopa\carbidopa in PD patients experiencing OFF episodes
Trials In Progress at UCSF for PD OFF

Repurposing Rifaximin

Microbiota Intervention to Change the Response of Parkinson’s Disease (MICRO-PD)

Phase II, Single Center, Randomized, Double Blind, Placebo Controlled Trial of Rifaximin

Goal: “Reset” Microbiome → Reduce OFF time

Rationale: Certain GI bacteria contain aromatic amino acid decarboxylases not blocked by carbidopa → reduced l-dopa absorption, Increased OFF; Eliminating these bacteria may reduce OFF time

Study Drug: Rifaximin

Mechanism: A rifamycin antibacterial w/ minimal systemic action

Eligible: PD, On l-dopa, Wearing OFF

Future Trial at UCSF for PD OFF Episodes – Neuroderm

Study Drug: ND0612 Sterile LD/CD solution w/ LD concentration 60 mg/mL and CD concentration of 7.5 mg/mL
- Administered as a continuous subcutaneous infusion over 24 h
- Infusion pump system CRONO TWIN ND

Inclusion

- Dx of PD
- Age ≥ 30
- Motor fluctuations w/ an average of 2.5 hours of “OFF” time daily (min 2h/day)
- At least 4 doses/day of LD/CD or 3 doses/day of Rytary and at least 400 mg/day of LD
- MMSE ≥ 24, H&Y ≤ 3

Exclusion

- Atypical/secondary parkinsonism
- Psychosis or troublesome hallucinations in the past 6 mo
- Hx of DBS, thalamotomy, pallidotomy
- Severe disabling dyskinesia
- Hx of skin conditions or inadequate SC tissue
Fracture Prevention in PD – Trial of Parkinson’s And Zolendronate - TOPAZ

- Fractures 2-4 fold increased in PD
- Only ~ 3 – 5 % of PD patients treated for osteoporosis

TOPAZ trial:
Goals: Reduce Risk of all clinically diagnosed fractures (primary), hip fractures (secondary); Reduce Risk of Total Mortality (exploratory); Safety of ZA in pts w/ PD

Design:
- 3500 men and women with PD, > 65, HY I-IV
- Single IV infusion of Zoledronic Acid (ZA), a bisphosphonate
- Randomized, placebo-controlled, double blinded
- Home-Based - No clinic visits; telemedicine assessments
ENROLLING NOW!

www.topazstudy.org 1-800-4PD-INFO
(1-800-473-4636)

Palliative Care Trial Results

Usual Care plus Multidisciplinary Palliative Care Clinic

Results:
- Improved Quality of Life
- Improved symptom management
- Reduced caregiver stress
- No added cost

JAMA Neurology, In Press 2020
UCSF Movement Disorders REFERRALS

- Clinic Referrals: 415-353-2311

- Research Study Participation:
  Danilo Romero
  Phone: 415-353-8328
  Email: Danilo.Romero@ucsf.edu