Predicting Cognitive Decline in Parkinson’s Disease

Cognitive decline and dementia are among the most disabling features of PD. Identifying risk factors for cognitive decline in PD could help in the development of effective treatments, and might ultimately lead to personalized treatment plans for people with PD. Liu and colleagues built a predictive algorithm for cognitive decline and for dementia in PD, based on longitudinal assessments of 2482 people with PD in 9 longitudinal cohorts from Europe and North American populations. Candidate clinical and genetic risk factors were chosen based on literature review. The risk score was developed in 1350 people with PD followed over more than 12 years, and replicated in 1132 people with PD followed over more than 8 years. The resulting clinical-genetic score had seven predictors. Age at disease onset was responsible for most of the variance (56.5%). Other factors had more modest contributions: enrollment MMSE score (7.7%), years of education (5.4%), enrollment motor score (MDS-UPDRS III) (4.7%), gender (2.6%), depression (1.9%), and \( \beta \)-glucocerebrosidase (GBA) gene mutation carrier status (1.5%). Using a pre-defined cut off, the risk of cognitive impairment within 10 years of PD onset was accurately predicted with an area under the curve (AUC) of >0.85, and the risk of dementia within 10 years of disease onset was predicted with an AUC of 0.877. High risk scores were linked to a more rapid decline in Montreal Cognitive Assessments over time (p < 0·0001). The sample size for a theoretical clinical trial testing a treatment to prevent cognitive decline in PD would be six times smaller if participants were selected using the risk score.

In an accompanying editorial, Aarsland and colleagues recognized this as a substantial new development, but cautioned that it is too early to implement in clinical practice. That noted that age at onset, by far the strongest predictor, is closely correlated with age, a factor long recognized to increase risk of dementia. Because the risk score performed best at ten years, rather than a shorter duration, clinical usefulness is reduced. The future addition of other gene mutations, biomarkers and imaging findings is expected to further improve the accuracy of risk prediction in PD.


The Role of Palliative Care in the Treatment of Parkinson’s Disease

Parkinson’s disease is life-limiting and carries a significant symptom burden that is likely to be amenable to palliative care clinical strategies. Palliative care focuses on relieving suffering through an interdisciplinary approach that addresses what the founder of palliative care, Dr. Cicely Saunders, called the “Total Pain” of serious illness. This includes a focus on providing intensive symptom management, as well as emphasis on psychosocial support, spiritual wellbeing, planning and preparing for the future, and reducing caregiver stress. In addition, palliative care sees dying as a natural and inevitable process, and addresses prognosis and advance
care planning to ensure that goals of care are met. Palliative care has been formally studied in randomized controlled trials in patients with cancer, congestive heart failure, multiple sclerosis, chronic obstructive pulmonary disease and interstitial lung disease. Outcomes of these studies include a reduction in overall symptom burden and caregiver stress, fewer hospitalization and invasive treatments at the end of life, significant reduction in the cost of care, and an improved survival and greater benefit in quality of life in those receiving earlier palliative care. Two randomized controlled trials of palliative care in Parkinson’s disease are ongoing.

A summary of the first Internal Work Group Meeting on Parkinson’s disease and Palliative Care supported by the Parkinson’s Disease Foundation was published in 2017 to review the evidence for this clinical approach, and to make recommendations regarding clinical research and practice. Strategies for widespread research and implementation of palliative care are discussed. A council of patients and care partners convened for this Internal Work Group meeting encouraged the introduction of palliative care upon diagnosis, and its role throughout the disease course. This group suggested using the term “Supportive Care” to help overcome the stigma and misperceptions about “Palliative Care”, which often prevent patients from utilizing these services, and providers from referring to these services. This modern approach to palliative care has been termed “simultaneous care”, and incorporates the principles of palliative care in all stages of the disease process.


**Neurofeedback Control in Parkinson’s Disease Patients**

Excess beta band oscillations (13-30 Hz) in neural local field potentials in sensorimotor cortical areas and its associated phase amplitude coupling with the basal ganglia have been identified as potential biomarkers of Parkinson’s disease motor symptoms. Modulation of this biomarker may be the mechanism by which deep brain stimulation reduces motor symptoms. The therapeutic role of modulating these dysfunctional neural networks in Parkinson’s disease is the basis of two recently published proof-of-principle studies.

Dr. Swann and colleagues describe their initial experience with a completely implantable deep brain stimulation device in 5 individuals with Parkinson’s disease that allows for chronic brain local field potential recordings and chronic stimulation delivery. This study showed that chronic multisite field potentials in humans is feasible. These recordings of beta band power and phase amplitude coupling between the sensorimotor cortical areas (using a quadriporal lead placed in the subdural space over the motor cortex) and the subthalamic nucleus (using a quadripolar deep brain stimulation lead) can theoretically be used to create a closed-loop deep brain stimulation system that is programmed to minimize these dysfunctional neural networks to optimize stimulation settings for improved motor symptom control, while minimizing battery drain.

In a related study, Dr. Swann worked with Dr. Khanna, and other colleagues, to investigate whether individuals with Parkinson’s disease could be trained to modulate dysfunctional neural networks beta band power via a neurofeedback game. In this setting, neurofeedback included real-time neural data acquired through invasive neural recordings. Using the Medtronic Activa PC + S system and the Medtronic Nexus-D communication link, three individuals with Parkinson’s disease and therapeutic deep brain stimulators that simultaneously provided continuous stimulation while recording and wirelessly streaming neural data played a neurofeedback game for 1-2 hours. All three individuals were able to modulate beta band power from sensorimotor cortical areas by
driving a visual cued target on a computer screen using live beta band streamed data. This was accomplished in a neurological lab setting and in the participants’ home environment. This study will inform future work investigating whether chronic neurofeedback training is a potential therapeutic tool in Parkinson’s disease.


Committee Activities

Clinical Care Committee

- **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The Philadelphia PADRECC leads the committee for June/July. The committee meets via conference call the first Tuesday of the month at 12pm (EST)

- **Standardize and Optimize Clinical Care:** The committee continues to discuss latest research on PD, new treatment strategies and a variety of clinical issues to improve patient care and outcomes. It also serves to provide clinical support to the consortium network by focusing on measures to standardize clinical care across the PADRECC network. Recent agenda items have included discussions on:
  1. The management of orthostatic hypotension including the role of the newly FDA-approved agent droxidopa (Northera).
  2. Continued discussion focused on clinical experience sharing among the group regarding DUOPA™ (carbidopa and levodopa) enteral suspension delivered directly into the small intestine for the treatment of motor fluctuations for people with advanced Parkinson's disease
  3. The prevalence of vitamin D deficiency in Parkinson’s disease and the need to monitor and adequately replete levels for bone and cognitive health.
  4. Practical aspects regarding the use of DAT scans; applications and pitfalls, including the issue of drug interference
  5. Continued discussion on the use of Pimavaserin (Nuplazid) in the treatment of psychosis associated with PD, compared to quetiapine and clozaril.
  6. Continued discussion of Rytary and conversion and titration dosing strategies. Consensus that often more than a three times/day dosing is needed.
  7. Discussion of the possible role for levodopa-induced hyperhomocysteinemia in Parkinson’s disease and the strategies to monitor and manage this problem

Education Committee

- **PADRECC/EES Movement Disorder Series:** The final audioconference for FY 17 will be held on September 14, 2017 “Cognition and Exercise” by Dr. Megan Gomez, PhD, Long Beach VAMC, West LA PADRECC. The audioconferences are archived on the National website [www.parkinsons.va.gov](http://www.parkinsons.va.gov) under the Movement Disorder Series tab. EES request has been submitted to continue the movement disorders series
for FY19.

- **National Newsletter**: The newsletter is currently being assembled.

- **Suggested Education Essentials Handout**: This hand-out has been updated and provides useful links to PD resources in the following areas: Overview of PD, Exercise, Medications, Nutrition, and PD Organizations. The handout can be found on the National Website, please share with your patients: https://www.parkinsons.va.gov/resources/EducationEssentialsNewlyDx.6.2017.pdf

- **Patient Education Brochures**: In response to the 2016 National VA PD Consortium Education Needs Assessment, the PADRECC Patient Education Brochures have been updated and are now available for download on the National Website. Please share with your patients: https://www.parkinsons.va.gov/patients.asp

- **National Website Maintenance**: The committee performs monthly maintenance checks of the National Website to ensure information is current and up-to-date.

- **“Mood Disorders in PD: What’s New”**: This enduring material project was done in collaboration with EES and is an on-line TMS self-study program that offers CME credit for a 3 year period. This program provides VHA healthcare professionals with a broadened medical awareness of Mood Disorders in PD. The program is available on TMS: https://www.tms.va.gov/learning/user/deeplink_redirect.jsp?linkId=ITEMDETAILS&componentID=14771&componentTypeID=VA&revisionDate=1343926380000

  *Please note CME credit will no longer be available as of July 30, 2017*

- **PADRECC Transmitter**: This committee continues to assemble and distribute this e-newsletter every other month.

**Dates to Remember**

**September 14, 2017**

**EES/PADRECC Movement Disorders Series**

**Topic**: Cognition and Exercise

http://www.parkinsons.va.gov/

**San Francisco PADRECC Updates**

- **First-of-Its-Kind Teleneurology Rotation for Residents at the San Francisco VA**

  *Nicholas B. Galifianakis, MD, MPH – PADRECC San Francisco*

Last year, the VA Office of Rural Health (ORH) funded an extra neurology resident position at the San Francisco VA (SFVA) to set up a new teleneurology training rotation. Nicholas Galifianakis, MD, Assistant Professor of Neurology at the University of California San Francisco (UCSF) and movement disorders neurologist at the SFVA PADRECC, whose career focus has been clinical research in telemedicine for PD, was asked to lead the efforts to develop and launch this novel resident rotation. This exciting development allows Neurology at the SFVA to build on VA’s mission to expand access to veterans, especially those who experience significant travel burden; both from geographic distance and neurological disability. It also
gives UCSF neurology residents (who all rotate through the SFVA) an opportunity to learn more about an aspect of patient care that is both cutting edge and an inevitable and invaluable part of future of health care delivery.

Now, each UCSF neurology resident will spend 4 weeks of their residency training rotating through VA neurology clinics (e.g. the PADRECC, the Epilepsy Center of Excellence, the ALS clinic, and general neurology clinics), caring for veterans exclusively via telemedicine technology. In the first two-week block, residents learn through didactics about teleneurology, hands-on practice with different telemedicine modalities and software platforms, and primarily learn through clinical experience, providing care to veterans via “virtual house calls” (directly into patient homes) and clinic-to-clinic encounters (known as VTEL’s at the VA), as well as performing remote e-Consultations. In the second two-week block, during their final year of training, they either contribute to ongoing teleneurology research projects, help develop or expand new clinical teleneurology services at the VA, or develop their own plan as to how they will implement telemedicine technology in their own future careers. With this comprehensive training, UCSF/SFVA neurology residents are already significantly expanding access to rural veterans. They are also poised to be future leaders in developing new, innovative models of neurological care delivery using technology.

- Expansion of Telehealth Clinics

Susan L. Heath, RN MS CNS – PADRECC San Francisco

VA PADRECC-SF Telehealth clinic visits with the State of California Veterans’ Home, Yountville, CA was established in 2016 and continues to thrive. The SF-Yountville model has been used for a VA Telehealth relationship with the State of California Veterans Home in Redding, CA. A remote general neurology clinic will be established and PADRECC-SF will offer movement disorders Telehealth visits.

VA California providers interested in understanding steps to creating VA Telehealth with California State Veterans’ Homes can call Susan Heath at PADRECC-SF (415) 379-5530.

- Parkinson's disease Palliative Care Clinic

Maya Katz, MD - PADRECC San Francisco

The Parkinson’s Disease Supportive Care Clinic at the San Francisco PADRECC Center of Excellence was the first Parkinson’s disease Palliative Care Clinic in the United States. Started 7 years ago, we continue to be pioneers in the delivery of interdisciplinary care focusing on alleviating the tremendous symptom burden associated with this illness to improve quality of life, align treatments with patient preferences, and reduce caregiver stress. Our experience with providing primary palliative care to those with Parkinson’s disease and related disorders is already forming efforts to spread this type of care to academic medical centers and community neurologists through several national and international grants.

For example, VA PADRECC-SF neurologists are starting a 5-year study that has been funded by the NIH to provide a palliative care model for Parkinson’s disease that can be widely disseminated. This study will assess the effectiveness and feasibility of a novel community-based intervention that empowers community neurology practices to improve care for Parkinson’s disease patients and caregivers through primary palliative care training, coaching and telemedicine resources. The primary palliative neurology training program for the NIH grant will be directed by the Education in Palliative and End-of-Life Care (EPEC)
education initiative. This training will also be a part of a larger online course available in conjunction with a textbook on neurology primary palliative care.

- **iMRI research**

  *Maya Katz, MD - PADRECC San Francisco*

Physiology-guided deep brain stimulation (DBS) surgery requires patients to be awake during a portion of the procedure, which is poorly tolerated by some patients. Interventional MRI-guided (iMRI) DBS surgery was developed by SFVA PADRECC Neurosurgeons Dr. Philip Starr and Dr. Paul Larson to use real-time image guidance, obviating the need for patients to be awake during lead placement. The primary reasons for choosing iMRI DBS is a preference to be asleep during implantation due to: 1) a history of claustrophobia; 2) concerns about the potential for discomfort during the awake physiology-guided procedure in those with an underlying pain syndrome or severe off-medication symptoms; or 3) non-specific fear about being awake during neurosurgery.

The SFVA is the first to formally study iMRI implantation using a stronger 3T magnet. Prior publications have used the 1.5T magnet, which is less applicable to most neurosurgical sites, which use the 3T magnet. Understanding the intricacies of this system using this more advanced magnet allows this groundbreaking technology to be used at a greater number of centers across the country to provide state-of-the-art care to individuals with Parkinson's disease.

Currently, the iMRI research study has completed data collection for its first 4 enrolled subjects and continues to enroll new subjects. To date, patients enrolled in this study have had comparable improvement in motor symptoms compared to the more traditional physiology-guided DBS lead placement.

- **Speechvive**

  *Maya Katz, MD - PADRECC San Francisco*

  Parkinson’s disease has traditionally been viewed as a disease of movement, but we now know that the most significant and disabling symptoms are the non-motor issues. Speech is markedly impaired for most people with Parkinson’s disease after about 5-10 years of disease duration. Primarily, this impaired speech is characterized by a hypophonia that makes it very difficult, and eventually impossible to hear what individuals with Parkinson’s disease are saying. This markedly contributes to the social isolation and disability experienced by those with this disease. As of January 2017, we are now offering the FDA approved Speechvive device, which uses a natural phenomenon called the Lombard effect to double the volume of patient's voices using a small externally wearable device.

- **Parkinson’s Support Group: Shake-it-up-Baby!**

  *Annie Li Wong, NP – PADRECC San Francisco*

The San Francisco Parkinson’s Support Group is a community group of about 40 patients and caregivers from all over the Bay Area who meet once a month at the SF VA. PADRECC advanced practice nurses Susan Heath and Annie Li-Wong co-lead the Parkinson’s patients and our Chaplain, Carolyn Talmadge, leads the caregiver discussions.
The SF PD Support Group joined the National Parkinson’s Foundation MOVING DAY Walk in San Francisco for the third year in a row. Captains Susan Heath, CNS and Annie Li Wong, NP lead their “SHAKE IT UP BABY” team to 6th place in fundraising. Their dedication to raising awareness for Parkinson’s disease raised almost $10,000.

- **Cortical Physiology of Deep Brain Stimulation on Motor Circuits in Parkinson’s Disease**

  *Philip A. Starr, MD, PhD, PADRECC San Francisco*

  While the patterns of neuronal loss in Parkinson’s disease have been well described, the manner in which neuronal loss alters brain circuitry to produce the cardinal motor signs of Parkinson’s disease has not been clear. The Starr lab work has revealed specific patterns of neural activity underlying the signs and symptoms of Parkinson’s disease (PD). We introduced powerful technical approaches for understanding circuit-level brain dysfunction in PD: electrocorticography, high-resolution, high-signal recordings from leads placed directly on the brain surface during surgery. We have used this technique to demonstrate an abnormal state of neuronal synchronization in the motor cortex, that is related to slow movement in Parkinson’s disease. We showed that an important mechanism of therapeutic deep brain stimulation is reversal of this abnormal pattern.