Multi-site PLS Natural History Study (PNHS)

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COLUMBIA UNIVERSITY
MEDICAL CENTER

History and Perspective

- PLS has been a very rare, puzzling, and obscured disease.
- PLS is considered as an extreme end of the ALS spectrum.
- We conducted a prospective 5 multisite PLS COSMOS study.
- PLSFRS (21 multisite-study) has been developed for the PNHS.
- International PLS Conference was held in 2019.
  - The PLS Diagnostic Criteria has been renewed and published.
  - PLS Conference Supplement is about to be published.
  - PNHS is now to begin!
  - Biennial PLS Conference in 2021 is planned (Sabrina).
- The first disease-modifying clinical trial is not any longer unrealistic or far-fetched.

Funding for PNHS

- ALS Association
- Spastic Paraplegia Foundation (SPF)
- Mitsubishi-Tanabe Pharma (MTP)
- Mr. David Marren and the Family
- MDA Wings for early ALS/PLS

SPF SPASTIC PARAPLEGIA FOUNDATION, INC.
Research / Education / Support

ALS ASSOCIATION

Mitsubishi Tanabe Pharma America

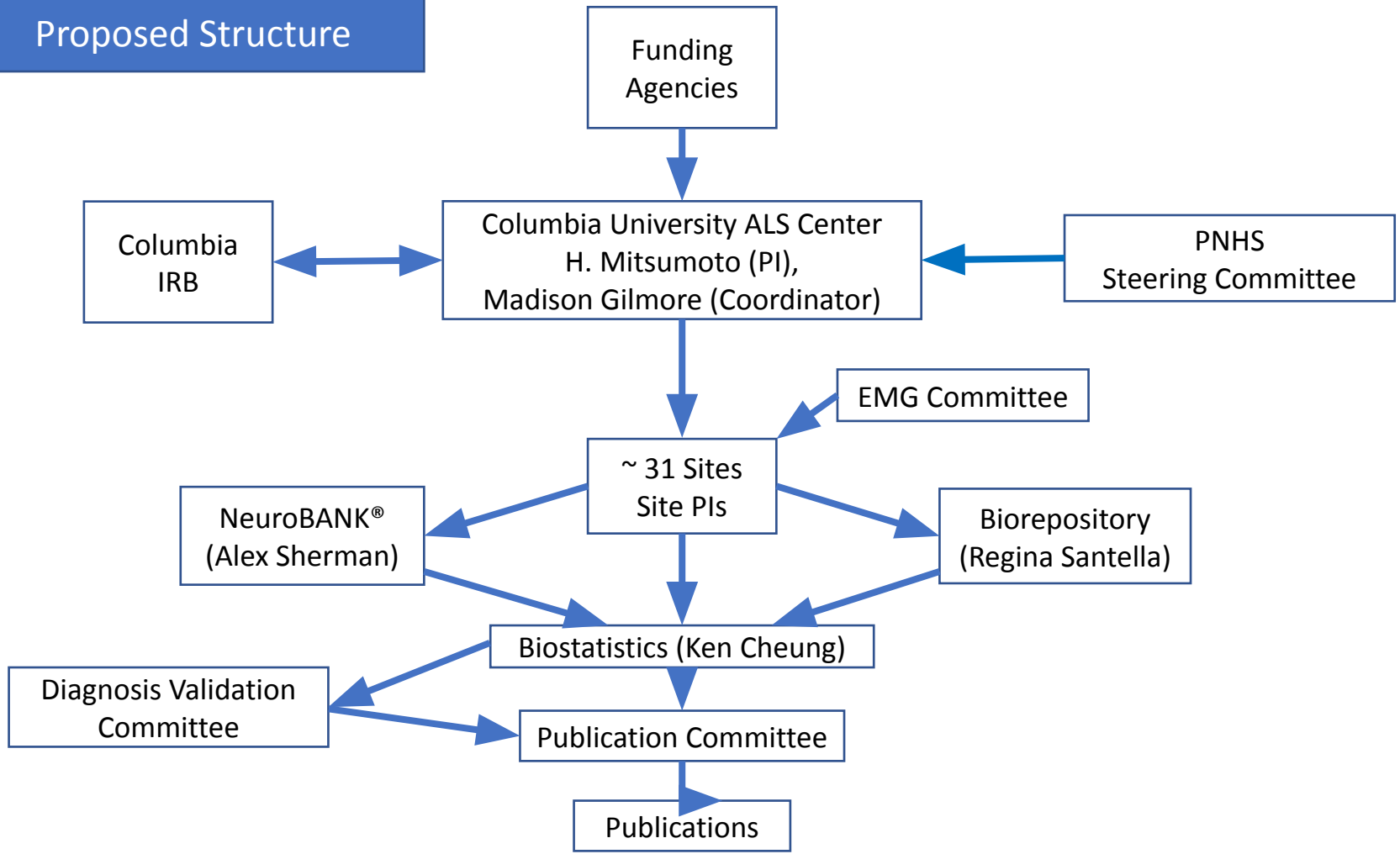
Study Objectives

1. To establish the natural history of 50 early PLS cases and 50 definite PLS cases
2. To validate the diagnostic accuracy of the new PLS diagnostic criteria
3. To conduct a power calculation for a future RCT and open-label investigation using historical controls based on this study

Participating Sites		
Site	Site PI	Site Name
1	Daragh Heitzman	Texas Neurology
2	Omar Jawdat	U of Kansas
3	Eric Sorenson	Mayo, MN
4	Stephen Goutman	U Michigan
5	Steve Scelsa	Beth Israel
6	Sabrina Paganoni	Mass General
7	T. Heiman-Patterson	Temple U
8	Nick Maragakis	Johns Hopkins
9	David Walk	U Minnesota
10	Christine N. Fournier	Emory U
11	Lauren Elman	U Penn
12	Nanette Joyce	UC Davis
13	Bjorn Oskarsson	Mayo, FL
14	Erik Pioro	Cleveland Clinic
15	Zachary Simmons	Penn State U
16	Ed Kasarskis	U Kentucky
17	Yaz Kisanuki	Ohio State U
18	J A Fernandes	U Nebraska
19	Ghazala Hayat	Saint Louis U
20	Jinsy Andrews/HM	Columbia U
21	Lorne Zinman	U Toronto
22	Ali Habib	UC Irvine
23	Justine Kwan	NINDS
24	Christen Shoesmith	WU, London, Ontario
25	Wendy Johnston	U Edmonton
26	Angela Genge	McGill U
27	Catherine Lomen-Hoerth	UCSF
28	James Wymer	U Florida, Gainesville
29	Kelly Gwathmey	VCU
30	Senda Ajroud-Driss	Northwestern U
31	Michael Pulley	U Florida, Jacksonville

US and Canadian Sites

Proposed Structure



Standing Committees and Objectives

1. Steering Committee (Alex, Angela, Dave, Frank, Hiroshi, Ken, Kuldip, Madison, Mary Kay, Sabrina, Zach)
   - Steer the entire project
   - Solve any unforeseeable issues or problems
   - Approve data and biosample sharing
   - Interpret results and guide publications
2. EMG Committee (members solicited)
   - Select muscles examined
   - Define LMN involvement
3. Publication Committee (members solicited)
   - Solicit publications
   - Review manuscript and approve for the PLSNHS group
4. Diagnosis Validation Committee (members solicited)
   - Study the final diagnosis at 12 months
   - Identify the difference between the original Dx and final Dx

Inclusion Criteria

- Adult participants (≥ 25 years of age)
- PLS diagnosis is based on the new PLS diagnostic criteria
- Symptom onset was no more than 15 years prior to baseline
- Ability to independently walk with or without an assistive device (e.g., walker) at the baseline evaluation
- In cases where a molecular test has been done prior to enrollment in this study, HSP or HSP-related mutations are negative
- Expected to have at least some bulbar symptoms (dysarthria, dysphagia, drooling or pseudobulbar affect); however, the absence of these symptoms will not exclude participants when molecular testing is negative for known HSP
- UMN symptoms and signs in a region other than the legs
- Normal brain and spinal cord neuroimaging except for changes expected for PLS
- No active major neurological diseases other than PLS and no history of major neurological diseases

Inclusion Criteria (Continued)

- No major unstable medical diseases that require treatment (e.g., active cancer, dialysis) in the past 6 months
- Residing within a commutable distance to the study site and willing to visit the study site as required
- No history of ALS or PLS in immediate family and no family history of hereditary spastic paraplegia (HSP)
- No significant lower motor neuron (LMN) degeneration upon the EMG examination within 12 months before enrollment (evident entrapment neuropathy or radiculopathy are acceptable)
- If an EMG test was not done in this period, an EMG should be obtained through regular patient care (through insurance) in order to make a diagnosis of PLS (this cost will not be covered by the research study)
- Participant understands the purpose of the study, has capacity to consent, and is willing to sign the informed consent form

Exclusion Criteria

- Unwilling or unable to give informed consent
- UMN symptoms and signs only in the legs
- Unwilling or unable to visit the study site as required
- Clinically obvious cognitive impairment that precludes obtaining informed consent, as determined by the site PI
- Participating in clinical treatment trials

Study Outline and 24-month Follow-Up

Evaluations	0	3	6	9	12	24
Eligibility Assessment	X					
Consent/Enrollment	X					
Physical Exam	X					
Neurological Exam	X				X	
Cognitive Testing*	X					
Equipment and Medication Review*	X	X	X	X	X	
Penn UMN Score & FVC	X		X		X	
PLSFRS*	X	X	X	X	X	X
Pa-ta-ka Test*	X	X	X	X	X	X
Finger & Foot Tapping*	X	X	X	X	X	X
ALSSQOL-SF* & Neuro-QoL	X	X	X	X	X	X
Timed Up and Go (TUG)	X		X		X	
DNA	X					
Blood	X				X	
Urine	X				X	
EMG (Needle Electrode)					X	

(*) To be completed remotely by
Columbia University

EMG (only NEE) at 12-month point
(A charge to the EMG Committee)

- NCSs were done at the time of the diagnosis of PLS and not repeated
- Selection of the muscle for testing (to be determined)
- Determining the degree of abnormalities:
  - Acceptable known entrapment neuropathy or radiculopathy
  - Allowed minimum signs of denervation
  - Fasciculations
  - Chronic neurogenic changes

EMG Testing for PLS Follow-up
only at 12 month-point

1. Leg: GC, AT, VL or VM;
2. Arm: 1st DI, B, Pron T;
3. Thor parasp below T5;
4. CN: TG or Mentalis.

Outcome Exams by CU Evaluators

- Cognitive Testing
  - Telephone Interview for Cognitive Status (TICS)
  - ALS Cognitive Behavioral Screen (ALS-CBS)
    (Christodoulou et al. ALS/FTD 2016; 17:482-488.)
- PLSFRS
- ALSSQOL-SF
- Neuro-QoL (PRO)
- Medicine and DME use
- Bulbar PaTaKa speech for 10 seconds
- Finger tapping for 10 seconds
- Foot tapping for 10 seconds

Recruitment and enrollment issues (early vs. definite PLS)

- “Early” PLS (less than 24 months after symptom onset) or only “probable” PLS?
- The PI strongly believes that we need to include all patients before 4 years after symptom onset
- How should we enroll patients:
  - 2 participants for definite PLS cases per site
  - 2 participants for early PLS cases per site
  - Competitive enrollment

Investigational Research

- Natural history data to be followed by clinical trials
- Diagnostic validation
- EMG changes in PLS
- DNA and molecular analyses to identify novel genes (Matt Harms)
- Urinary OS biomarkers (Regina Santella)
- Novel biomarkers (studies are wide open)

DNA Studies (Matt Harms)

- C9 determination by repeat-primed PCR
- Identify pathogenic genes (fALS, HSP and PD)
  - Exome or panel HaloPlex
- Genome sequencing as a future study

- **NOTE:** The results of the genetic tests will be reported to the investigators –not the patients. If the investigators wish to report to their patients, they will have to obtain a formal diagnostic test at the available diagnostic lab. Our genetic tests are completely investigational; therefore, we are not responsible for reporting the results to the patients themselves.

Biostatistical Analyses (Ken Cheung)

- Analysis goals:
  - Characterize the natural history of the two patient cohorts
  - Provide information for future RCT
- Primary outcome: PLSFRS (primary)
- Longitudinal outcomes: Pa-ta-ka test, Neuro-QoL, finger tapping, etc.
- 3 visits (Site) or 6 visits (CUCC) including baseline
- Analysis using generalized linear mixed effects model:
  - To estimate decline rate (linear and non-linear)
  - To examine differences between the two patient cohorts
  - To account for participant characteristics (e.g. age, onset, cognitive test, etc)

Data Management NeuroBANK®
Alex Sherman

Summary and Conclusions

- This will be the first, comprehensive, prospective natural history study for PLS.
- We will study 50 early (0 to 48 months from symptom onset - probably ALS) and 50 definite PLS for 48 months and after symptom onset) for a period of 24 months
- This will be a large multisite (~33 centers) study.
- PLS-specific PLSFRS will be the primary outcome and the secondary outcomes will include Penn U UMN scale, FVC, TUG, finger and foot tapping, ALSSQOL, NeuroQOL, and EMG (12 months).
- We will analyze underlying genetic diseases and biorepository.
- We will use heavily telephone-based outcome
- We hope that out study will be followed by the first clinical trial for PLS