Cure Lafora Epilepsy Meeting
Center for Curing Epilepsies
September 6, 2015, 1:00 PM – 2:30 PM
Hyatt Macka Palace, Istanbul, Turkey

Present: Antonio Delgado-Escueta, MD, PhD (VA Greater Los Angeles & University of California, Los Angeles, Los Angeles, CA, USA), Viet-Huong Nguyen, PharmD, MPH, MS (Chapman University, Irvine CA, USA), Miljana Kecmanovic, PhD (University of Belgrade, Belgrade, Serbia), Marco T. Medina, MD (National Autonomous University of Honduras, Tegucigalpa, Honduras), Charlotte Dravet, MD (Catholic University Hospital, Rome, Italy), Kazuhiro Yamakawa, PhD (RIKEN, Brain Science Institute, Saitama, Japan), Roberto Michelucci, MD, PhD, IRCCS-Institute of Neurological Sciences of Bologna, Bologna, Italy), Pierre Genton MD (Marseilles, France), Javier Salas-Puig, MD, PhD (University Hospital Val d'Hebron, Barcelona, Spain) , Thierry Grissar, MD, PhD (University of Liege, Liege, Belgium), William Whitehouse, MD (University of Nottingham, Nottingham, United Kingdom), Ahmad Beydoun, (American University of Beruit, Beruit, Lebanon), Maher Arabi, MD (IBN Sina Hospital, Kuwait City, Kuwait), Manpreet Kaur, PhD (Jawaharial Nehru Center for Advanced Scientific Research [JNCASR], Bangalore, India), Sanjib Singh, MD (National Institute of Mental Health and Neuro Science [NIMHANS], Bangalore, India), Andrea Daga, PhD (E. Medea Scientific Institute, University of Padua, Padua, Italy), Laura Guilhoto, MD, PhD (Federal Univ of San Paulo, San Paulo, Brazil)

WELCOME AND INTRODUCTIONS

- Dr. Delgado-Escueta led the welcome and introductions for this meeting on the Lafora Disease/Epilepsy Cure Initiative.
- Dr. Delgado-Escueta explained the purpose of the meeting: (a) to bring together clinicians and scientists working on Lafora disease/epilepsy (LD) in order to assemble an international cohort of Lafora patients for disease characterization; (b) to prepare for clinical trials concentrated at major and minor study sites.
- **Our ultimate goal, shared by all, is to deliver curative molecules to all patients with Lafora disease. This means that all of you attending this meeting here (and many more future colleagues), will be conducting the actual clinical trials for the curative molecules. This will be a global effort. Our job is to organize us into a global consortium, organize and get patients ready for clinical trials, and prepare grant applications to the NIH.**
- To prepare for clinical trials, we would apply for an NIH grant that could support: (1) a central data bank of patients with Lafora disease worldwide; (2) development of outcome measures that would be used during clinical trials (e.g. outcome measures could include effects of treatment on BOLD fMRI, brain MRS, video-EEG electro-clinical phenotypes, laforin/DSP and malin/U3 ligase assays in fibroblasts or iPSCs); (3) development of a Lafora epilepsy disease progression scale; (4) examination of genotype-phenotype correlations that could impact clinical trials; (5) an early diagnosis campaign.
- Each participant was given a flash drive containing: (a) Meeting Agenda; (b) Curing Lafora Intake Forms from LA and; (c) Curing Lafora Follow-up Forms from Madrid and LA.

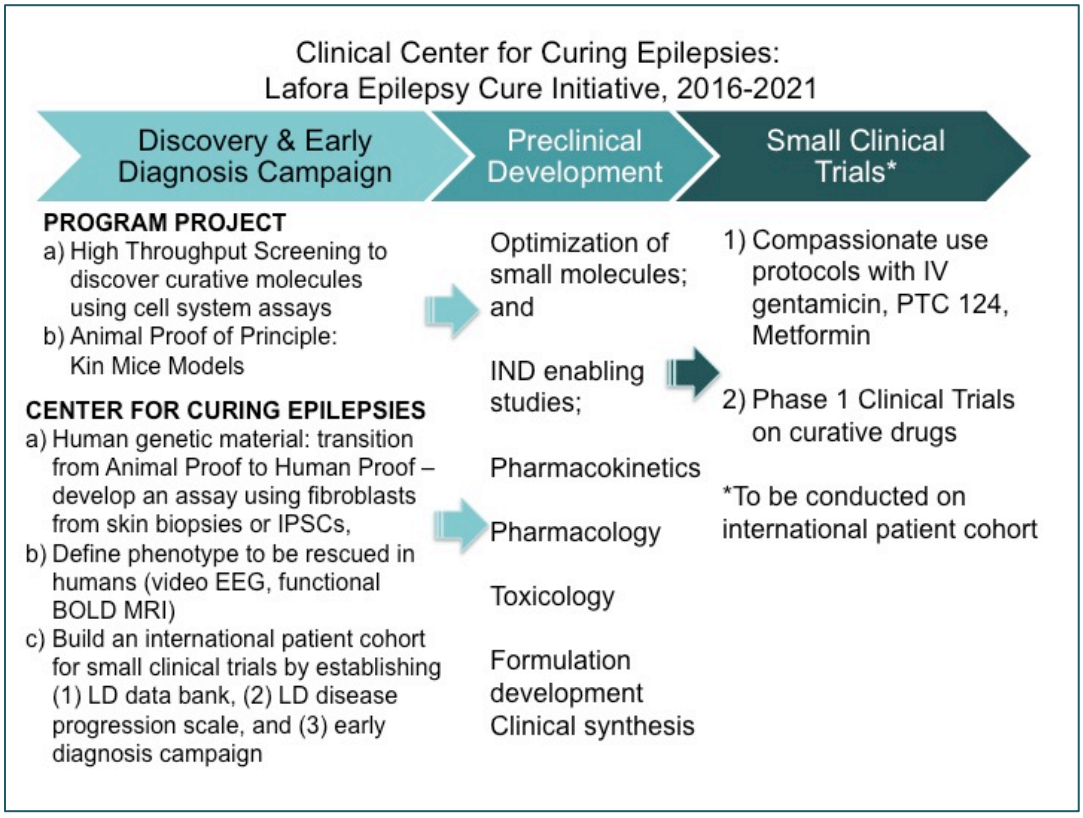
GETTING TO MEET AND KNOW EVERYONE" and PRELIMINARY GLOBAL SURVEY

- Each participant introduced themselves and briefly discussed their experience with Lafora epilepsy including the number of Lafora patients they have had in the past and how many LD patients they have who are still living and could participate in a clinical trial if a curative molecule was available.
    - Dr. Kecmanovic (Serbia): 7/7 patient still living
    - Dr. Medina (Honduras): 3/3 patients still living
    - Dr. Michelucci (Italy): 3/10 patients still living
    - Dr. Genton (France): 8/20+ still living
    - Dr. Salas-Puig (Spain): 2 patients still living
    - Dr. Whitehouse (UK): 2/4 patients still living
    - Dr. Beydoun (Lebanon): 5/10 patients still living
    - Dr. Arabi (Kuwait): 2/2 patients still living
    - Dr. Sinha (India): 4/10-12 patients still living
    - Dr. Guilhoto (Brazil): 1/5 patients still living
    - Total: 37 Lafora patients still living
- Dr. Delgado-Escueta commented that with the sporadic cases of LD patients presently living in various parts of USA, Mexico and South America, Greece and Turkey, Austria and Netherlands, the total could easily reach 50 patients. Drug trials in Cystic Fibrosis usually numbered 35 to 40 patients.

PRESENTATIONS

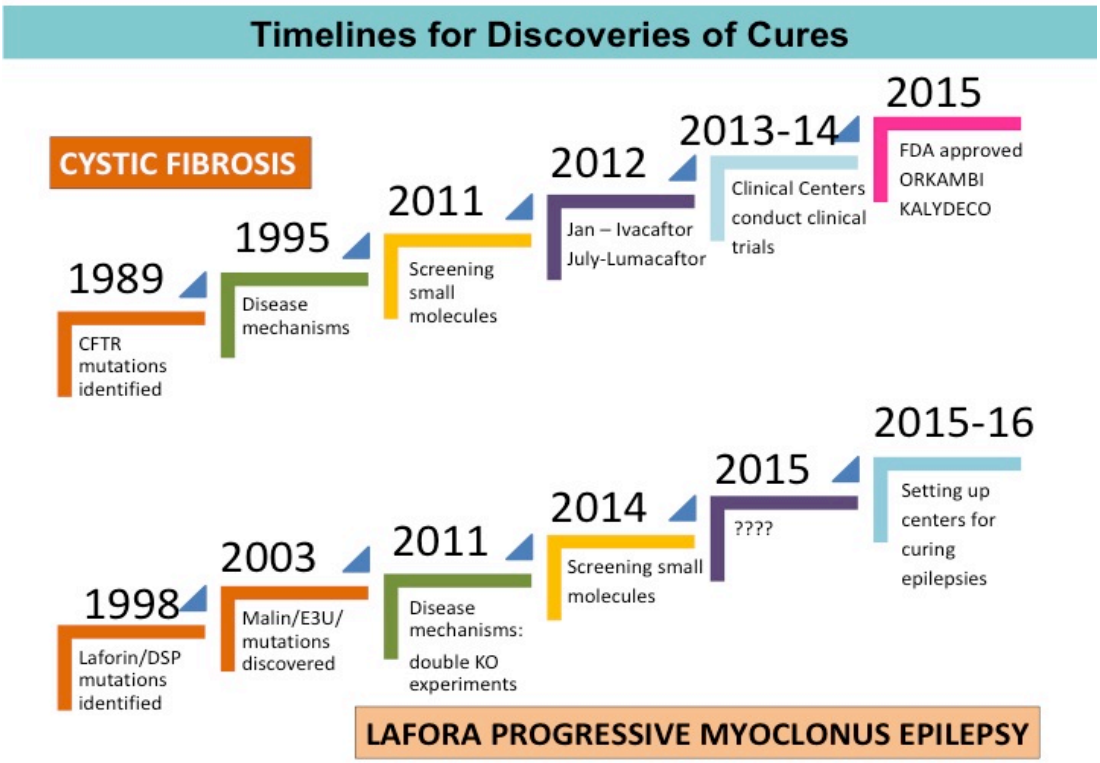
Animal proof of principle:

Dr. Delgado Escueta introduced the animal proof of principle that is the basis and stimulus for our present clinical endeavor. First, Minassian and colleagues from Toronto showed in double KO experiments that in laforin KO mice the disease could be rescued by knocking out PTG (protein targeting gene) and these mice exhibited reduced Lafora body accumulation, and rescue of neurodegeneration and myoclonic epilepsy.



Guinovart and his team from Barcelona observed the same results when malin-deficient mice had their PTG knocked out. This nearly completely eliminated Lafora bodies and rescued neurodegeneration, myoclonus, seizure susceptibility, and behavioral abnormality. The final question then was---which of the proteins/genes that targeted the PTG site was the crucial protein/gene that was responsible for the formation of Lafora bodies and the ensuing neurodegeneration? Roach, with Anna diPaoli-Roach and Tagliabracci then zeroed in on glycogen synthase and knocked it out in malin-deficient mice. Malin-deficient mice lacking glycogen synthase (GYS1) were devoid of LBs, exhibited normal electrophysiological properties, were not susceptible to kainate-induced epilepsy, and did not exhibit increased neurodegeneration. If only one GYS1 allele was knocked out in malin deficient mice, rescue of the phenotype was only partial. These experiments showed that LD in mice was curable. If so, LD must also be curable in humans.

TIMELINES FOR DISCOVERY:

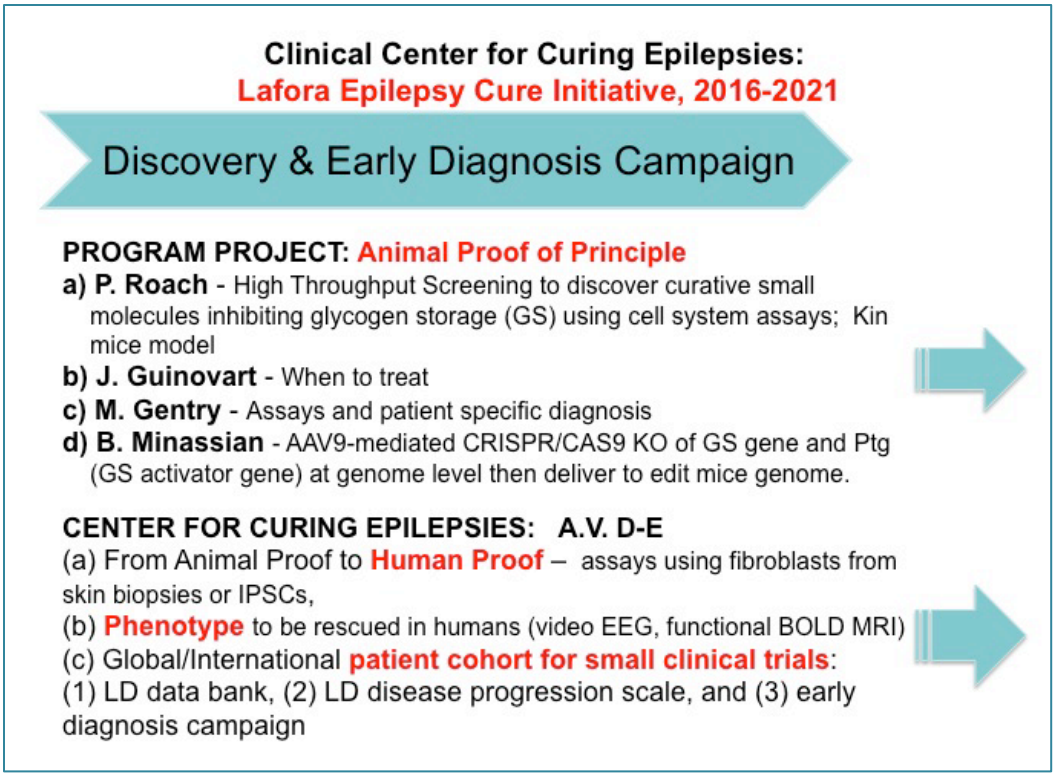


Dr. Delgado-Escueta explained that optimization of the curative molecules (e.g., pharmacokinetics, pharmacodynamics of the small molecules, optimization for human use, etc) could happen quickly and could possibly occur simultaneously with the above preparations for clinical trials. Therefore, we would have to really "pony fast on our horses" and get the global cohort of LD patients ready for curative drug trials. At this point, D-E shared a slide depicting time scale that transpired during the development of curative drugs for cystic fibrosis. With $20 million from their foundation and a partnership with a pharmaceutical company, cystic fibrosis researchers developed and conducted clinical drug trials in 4 years (FROM 2011 TO 2015). The FDA approved two curative drugs for cystic fibrosis this past July, 2015. Our timelines may not be as rapid because we have to write grants and apply for NIH funds for: (a) the initial phase of the drug discovery of small molecules; (b) the preparation of the global cohort for the drug trial; (c) optimization of small molecules and; (d) the actual clinical drug trials.

LAFORA DISEASE/EPILEPSY CURE INITIATIVE

- Dr. Delgado-Escueta then explained that the Lafora Disease/Epilepsy Cure Initiative has two parts for the next 3 to 5 years: (1) a program project that develops the curative molecules and elucidates their basic mechanisms and then; (2) development of a clinical center for curing epilepsies that would prepare for the execution of the clinical trials for the curative molecules. M Gentry, B Minassian, J Guinovart and P Roach are submitting the program project component of the Lafora Disease/Epilepsy Cure Initiative in October 2015. This application will support four component projects including: (1) high throughput screening for discovery of small molecule inhibitors of glycogen storage in cell systems and through the kin mice model to be led by Dr. Peter J. Roach (Indiana, USA); (2) investigation of appropriate time to treat to be led by Dr. Joan Guinovart (Barcelona, Spain); (3) investigation of diagnostic assays and patient specific diagnoses to be led by Dr. Matthew Gentry (Kentucky, USA); (4) and investigation of gene therapy in glycogen synthase knockout mice (e.g. through reintroduction of PTG a glycogen synthesis activator) led by Dr. Berge Minassian (Toronto, Canada).

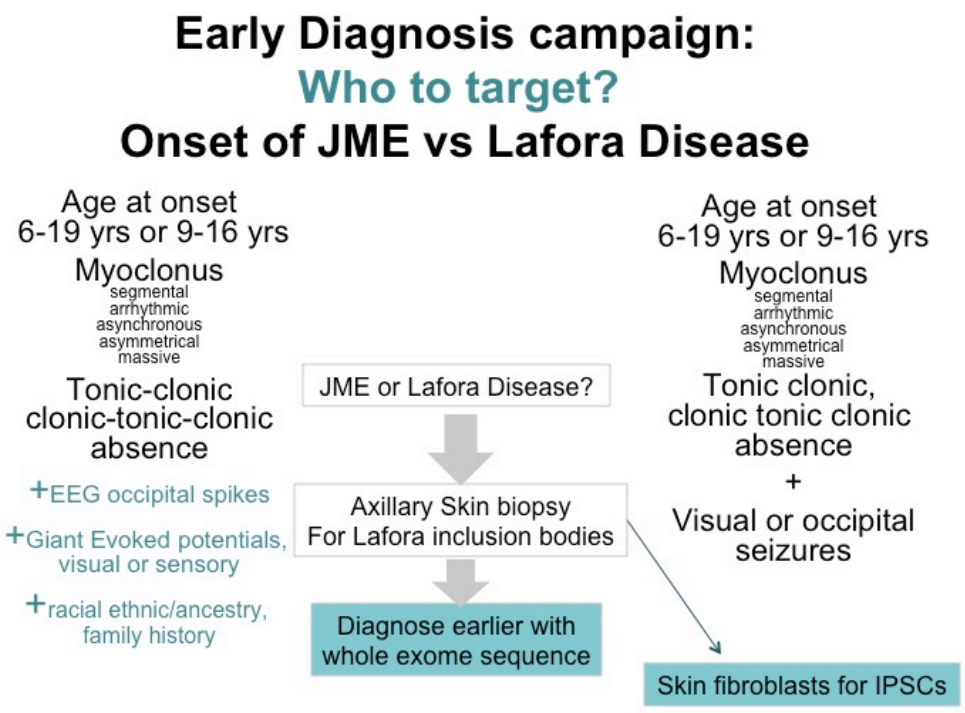
- Dr. Delgado-Escueta then explained our purpose for the present gathering---to develop a center for curing epilepsies. The first epilepsy we will cure is Lafora disease. This clinical center will compliment the program project application and execute the clinical trials for the "well validated curative molecule". Hopefully, we can apply to NIH for such a clinical center in 2016. The center for curing epilepsies will be led by A.V.D.E., M. Gentry, JM Serratosa, B. Minassian and those of you who wish to play a bigger role in administering the center. Understandably, we would welcome those of you who have a large population of LD patients to play a bigger role in the center and the clinical trials.



- Dr. Delgado-Escueta listed as aims for the center: (1) development of assays to establish proof of principle in humans such as using fibroblasts from skin biopsies or assays with IPSCs to ascertain treatment effect; (2) ascertainment of treatment effect on phenotype via video EEG, functional BOLD MRI; (3) establishing a global/international patient cohort for small clinical trials; (4) establishment of an international LD databank; (5) further development of an LD disease progression scale; (6) development of an LD early diagnosis campaign.

OPEN FLOOR DISCUSSION

Early diagnosis campaign:



- Dr. Javier Salas-Puig (Barcelona) led a spirited discussion on the early diagnosis campaign. Javier started by reviewing the slide on LD early diagnosis campaign (provided to the participants on handouts and in flash drive) and led the open floor discussion on the early diagnosis campaign. The issues are -- will treatment work only in the early stages of LD before neuroanatomical structures are destroyed? In the 2nd to 4th year of LD? Or will it work at all after 16 years of age? How about before the clinical phenotypes appear?

- Dr. Javier Salas-Puig (Barcelona) asked/discussed who should we target for an early diagnosis? All adolescent or preadolescents with the triad of grand mal, absence and myoclonic seizure? — as described in the slide. This would include a lot of Juvenile myoclonic Epilepsies! All agreed. Should we add those with occipital seizures to the triad? Several suggested this and all agreed that we should.

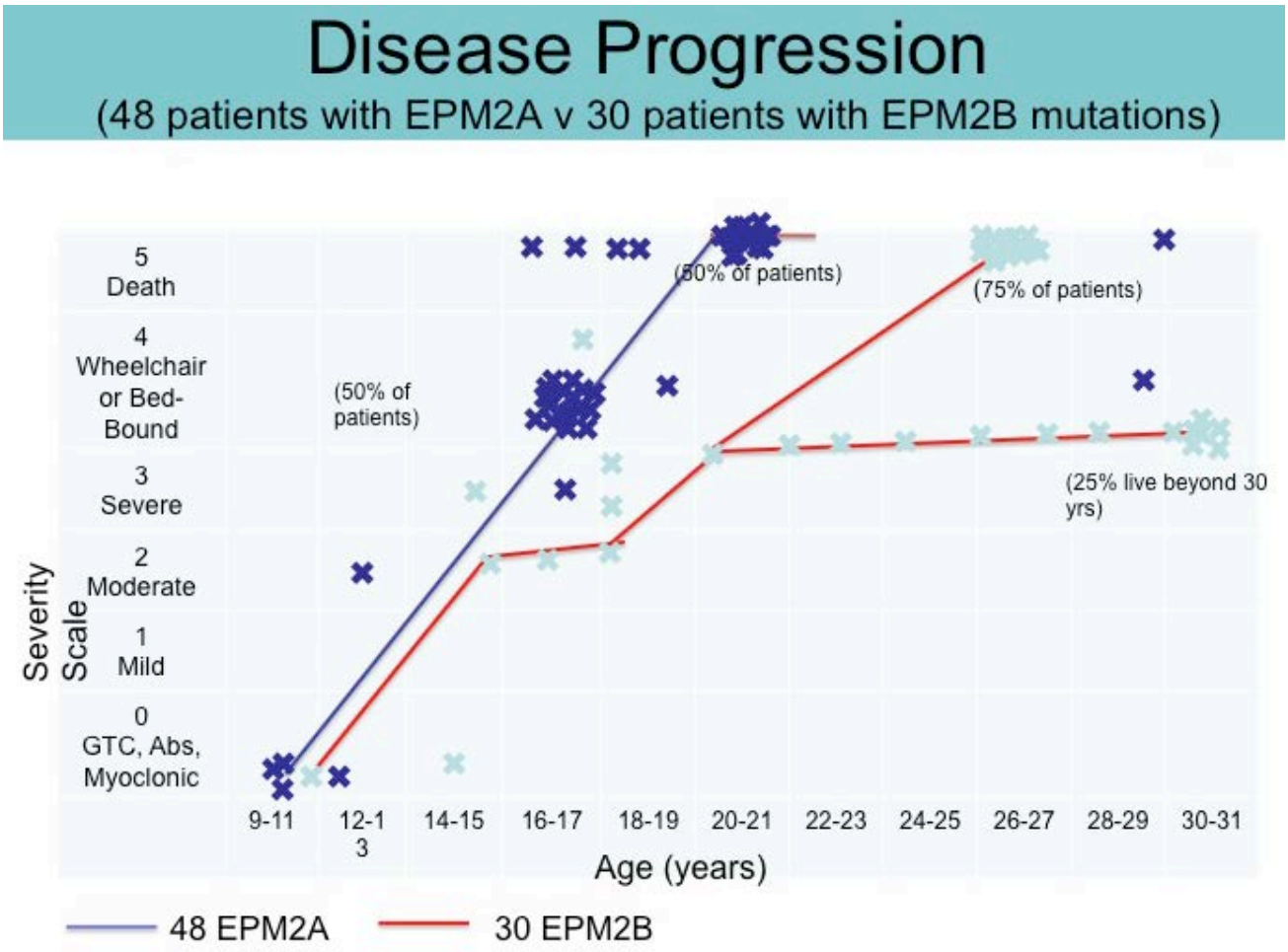
- Dr. Pierre Genton (Marseilles), then Dr. Sinha (Bangalore), Dr. Beydoun (Lebanon), Dr. Dravet (Marseilles) and Dr. Michelucci (Bologna) openly discussed and then agreed that patients with myoclonic seizures plus occipital spikes on EEG be targeted for the early diagnosis campaign. Opinions were sought from all attendees. All agreed with Dr. Genton's original point that patients with the triad of absence, grand mal, and myoclonic seizures may not have actual occipital seizures when they present, but if they have EEG occipital spikes or giant evoked potentials or a particular racial/ethnic/ancestral and family background -- they should be targets of the early diagnosis campaign.

- The early identification of presymptomatic siblings of the probands who carry the mutations of EPM2A or EPM2B was discussed. It was discussed that probands may be refractory to treatment but could still be used as a comparison group for their siblings.

- **It was concluded and agreed by all that education of neurologists was necessary to identify Lafora patients early.**

Lafora Disease Progression Scale:

- Dr. Nguyen showed the slide that explained what factors are used to diagnose the stages of Lafora disease – this is based on documented disease progression in 78 patients with either EPM2A or EPM2B mutations according to the age of the patient. Several cautioned that during the disease progression, seizure phenotype in Lafora might change with treatment such as negative myoclonus occurring with valproate treatment. The need for structured behavioral assessments was also discussed.



- Dr. Nguyen reviewed the LD disease progression scale and other scales in the intake and follow-up forms including the ataxia scale, the Montreal Cognitive Assessment Scale, the Katz Index of Independence in activities of Daily Living, and the Quality of Life for Alzheimer's Dementia assessment form. Suggestions for a more detailed modified disease progression scale were made. Suggestions for the addition of a normal baseline to the scale were made. Discussion concerning the criteria for classification of the asymptomatic patient with an abnormal EEG was made. Suggestions to using a point-based scale for disease progression was made with +1 point for a positive EEG, +1 point for other criteria. The suggestion of adding imaging and EEG findings into the LD disease progression scale were made and the point that bold functional MRIs are done in the Marseilles patients regularly at the request of Dr. Genton was made, although this would be difficult to obtain in Lebanon, Morocco, and Algiers due to funding.

LAFORA CURE INITIATIVE´S DISEASE PROGRESSION SCALE

Normal (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)	Wheel chair or bed bound (4 points)	Death (5 points)
No neurological signs or symptoms	A. Mild cognitive B. Mild ataxia (2) C. Preserved daily living activities D. Present interpersonal and family relation	A. Cognitive decline B. Moderate ataxia (3) C. Limited motor activities D. Preserved but limited social interaction	A. Mental impairment ("dementia", "mutism") B. Severe motor impairment C. Impaired daily living activities D. Poor social interaction	A. No significant daily living activities B. No social interaction C. Gastrostomy / tracheostomy	

Intake Forms and Follow Up Forms

- Dr. Nguyen reviewed the Lafora Intake and Follow-up form (provided to the participants on handouts and in flash drive). Suggestions to intake and follow-up form were made such as: including measures on cerebellar signs and speech including characterization of cerebellar atrophy as well as cortical atrophy as surrogate measures of disease progression, somatosensory evoked potentials done for all patients in a systematic manner as they may be done differently at different institutions, suggestion for EMG follow-up as well as video EEG follow-up.
- **Members of the group requested access to study protocols and consent forms and advise and help getting approvals from IRBs.**

CONCLUSION AND ACTION ITEMS

- Dr. Delgado-Escueta led concluding remarks and summarized what we have to do in the immediate future. To develop an international cohort, the following "nuts and bolts" work have to be done:

ACTION ITEMS-

(1) Protocol development: modify the present Lafora disease protocol to include a future clinical trial and modify consent forms and share this with all study sites for their contributions.

(2) IRB approval: work with all study sites IRB-- this will take manpower from our central LA site which we don't have and perhaps we can find a way to share the work of helping study sites get IRB approval (e.g.— Dr. Javier Salas Puig and Dr. Pierre Genton help European sites, Prof. Beydoun help Middle East sites, Prof. Sinha help India and Pakistan sites, Prof and Dean Medina help Latin American sites etc).

(3) Outcome Measures: develop valid outcome measures-- to do this we have to (a) refine the LD phenotype (e.g. characterize BOLD fMRI and other brain functional imaging) and (b) develop fibroblast culture from all patients. We need study site contributions for this.

(4) Early diagnosis campaign and data bank: we need feedback on the slide about early diagnosis. To get the data bank started, study sites should fill out a shortened version of intake forms for each living LD patient.

(5) Protocols for study sites: D-E and VHN will send study protocols and consent forms and uptake/ intake forms and follow-up forms to all study sites; feedback is critical before finalizing forms.

(6) Letters of participation: NIH has bullet points they require in letters of collaboration and VHN will work with study sites to help compose such letters of support/participation for application to NIH.

(7) Budget: Given what the study sites know now (e.g. what we need to do to prepare for the clinical drug trials), study sites should start discussing at their institutions what their budget needs will be -- e.g. skin biopsies for fibroblast culture, BOLD fMRI, whole genome sequencing for the early diagnosis campaign etc. Please discuss with and send D-E such budgetary needs which we will consider for the NIH proposal.

- **NEXT MEETINGS:**
- (1) Philadelphia at the American Epilepsy Society Meeting (Dec. 2015). The major items for discussion will be the steps needed to get IRB approval.
- (2) American Academy of Neurology, Vancouver, Canada, April 2016.
- At the end of the meeting, a group picture was taken with meeting participants (absent from photo: Dr. Yamakawa)

Note: Some things included above may have been added as supplementary information and may not have been discussed at the meeting due to limitations of time.