

“When you think you’re not strong enough to withstand the storm, become the storm!”

OT Clinical Studies Phase III at UNMC Omaha, September 25-29, 2017 Gait, Balance and Coordination Assessment in Patients with Orthostatic Tremor

It is important to note that ALL professionals involved with this study, and there were close to 90, volunteered their time – this in itself is truly amazing! They all made us feel so welcome and it is obvious they are passionate about helping us with this disease.

Led by principal investigator and neurologist Diego Torres-Russotto, MD, Phase III was the largest study ever conducted anywhere in the world on Orthostatic Tremor and the only longitudinal study ever (people who participate in more than one phase to follow progression) and included the following protocols:

- Investigating gait and posture changes using a suit with EMG (electromyography) surface sensors attached to the lower legs to measure gait speed while walking normally and briskly, on a treadmill and over ground, as well as balancing while standing quietly.
- Changes in brain structural networks via MRI-guided transcranial magnetic stimulation to map any lesions that might be related to OT.
 - fMRI of the brain while performing various activities and resting quietly
 - TMS to compare the sensitivity of different brain locations responsible for control of the upper and lower extremities, using surface EMG measurements
- Neuro-Ophthalmology Examination – completing a questionnaire on visual functioning and several examinations of visual acuity and eye movements using videonystagmography (VNG)
- Surface EMG signals on lower legs measured while sitting and standing and while undergoing a Visual Reality (VR) Experience consistent with fast movement, exposure to heights and sensation of instability or falling.
- Neurological Examination (walking, tracking, interrupted balance, leaning, standing).
- All participants completed the consent process and an extensive on-line 400-variable survey.

Peggy, assisted by Mary, Jane and Nina, efficiently organized and disseminated pre-event information to the Study participants and collaborated with Dr. Torres-Russotto and his team to further the research into the causes of Orthostatic Tremor. Staying mostly at the Element Hotel were 52 OT patients and 33 controls who participated in the many, many tests conducted September 25-29 at UNMC.

Dr. Torres advised that Dr. David Whitney offered to co-ordinate approximately 1,000 appointments that took place over the week.

Dr. Torres’ assistant, Arianne Marcoux sent out a personal agenda to each person attending, advising of their appointments. She was also on hand for some at certain locations, explaining the procedures, answering our questions, providing directions and offering delicious box lunches each day at the different test locations.

The Element and UNMC provided shuttle transportation along with participants who drove their own vehicles. Thank you to all – clinicians, associates and volunteers who ferried us to and fro during the week!

SYMPOSIUM HELD WEDNESDAY AFTERNOON AT THE BUFFET CANCER CENTER

Highlight of the week was the 4.5 hr. OT Research Update and the following is a summary of presentations which includes questions and answers asked to the doctors.

Dr. Torres-Russotto: Symposium Introduction

- A rare disorder like OT can shed really important light on other movement disorders.
- At UNMC, Dr. Torres leads these approximate 90 professionals working on 12 different research projects all of which are involved in this study.
- People from around the world have been participating in the study since 2012 (Phase I).
- Dr. Torres broke with conference protocol and took out his cell phone for a selfie with all of us in attendance!

Dr. Amy Hellman – General Overview of Orthostatic Tremor

- Defined tremor as an oscillating involuntary movement of a body part and which can be challenging to diagnose.
- OT patients experience unsteadiness when standing but rarely fall.
- Falls occur in elderly people who may have additional neurologic problems to which OT might be a contributing factor.
- Dr. Kenneth Heilman was the first MD to identify OT and published in 1984, described as sporadic, rare, occasional and not genetic.
- Dr. Elio Lugaresi in 1968 observed a patient unable to stand which was the first published description of OT.
- OT is more common in females (65-70%) with mean age of onset in the sixth decade. Earliest reported case is 13 years. Latest is 85 years.
- 25% of OT patients report improvement after drinking a moderate amount of alcohol.
- Mostly, OT is not familial (genetic).
- Common range of tremor is 14-18 mhz.
- 15% of OT patients feel they have severely worsened over time.
- 10% have tremors in other body parts.
- Why UNMC? UNMC is listed consistently in the 50 top Neurology Centers in the country.
- Cost of studies conducted and data compiled this week (without donated time) would be about \$500,000 and will take five years to analyze.
- Dr. T-R has developed a cell phone app to diagnose OT.
- Any physician can send an email with a video to UNMC for an answer and analysis.
- The OT Survey is so powerful it can answer the question whether or not the person has OT.

Q: How many OT patients have no trouble standing in waist deep water in a swimming pool?

A: 50%.

Q: Is there a correlation between head or spinal trauma and OT?

A: Something to consider.

Q: What are you doing to educate general practitioners and primary care physicians?

A: Presenting findings on OT all around the world.

Dr. Danish Bhatti: How is OT Diagnosed?

- OT may not be as rare as we once thought. Need to think outside the box.

- UNMC sees about 6000 patients a year with movement disorders.
- Currently we use EMG, measure MHZ, observe stance.
- Physicians don't even know what questions to ask/no standard set of questions exists.
- Tremor doesn't always show up, early on.
- Of 434 cases on line at PUB MED, only 15% specifically spoke to tremor, 52% mentioned a sense of instability.
- Balance Clinic in Sweden saw 701 patients with balance issues, but only five had OT.
- UNMC is looking at gait, balance and coordination in OT patients.
- EMG is always conducted on patients lying down (when OT symptoms are absent!).
- We are diagnosing OT too late.
 - Use posturography (standing on one leg and other indicators).
 - Smart phone app is an accurate measurement.
- How should we diagnose OT?
 - Do we even understand OT?
 - Is it a phobia of falling?
 - Ask about other symptoms.
 - Is OT truly orthostatic?
- Does OT go away when the patient is supported by water?
- Does it go away during the touch of electrical charge?

Q: Is there a hormonal connection to OT since the majority of patients are post-menopausal women?

A: Don't know.

Q: when patient is standing on one leg, does the tremor go away in the non-supporting leg?

A: Severity of tremor lessens as weight is removed.

Q: Would it help OT to have electrical stimulation of the legs?

A: This does not make the tremor go away. Stimulation of the brain is also being studied.

Q: Is there a racial component? (All attending this study are predominantly Caucasian).

A: Over 40 different countries have reported cases.

Q: When a person with OT bumps into someone, is there an increase in instability?

A: Yes, especially when the patient starts and stops. But this hasn't been specifically studied.

Q: Do you have a gut feeling of what's happening with OT?

A: Deferred to Dr. Torres.

Dr. Diego Torres-Russotto -- What Causes Orthostatic Tremor

Q: Is OT related to dystonia?

A: There are four criteria for dystonia, most of which are true for OT.

How do scientists find the cause of an illness?

- Opinions of experts.
- Studying the patient's history and the family history.
- Associations with other illnesses.
- Could be sporadic or just bad luck.

What do we know?

- It's a rare disorder.
- It affect females about 70%, males about 30%, most older than 30.
- It responds to Clonazepam.
- 74% of patients denied having falls.
- 78% of patients report disease progression.
- Most patients have no other abnormalities.
- Syndromic Associations were not conclusive.
- 10% of elderly have tremors but do not have OT.
- It's rarely reported as a family illness, but have found a few twins and triplets reported as all having OT.

How do we know if there are other signs?

- Ataxia (clumsiness) was universally found in OT patients.
- This means pathways in the cerebellum are abnormal in OT patients.
- Data from people who come to OT studies is different from the general population.
- 7% of OT patients are depressed.
- OT patients have high levels of anxiety.
- Most commonly used drugs are Clonazepam and Gabapentin.
- What are we doing for testing?
 - MRI, TMS, EMG, Visual Examinations.
- Conclusion: OT is a rare, often undiagnosed disorder with female predominance in patients of all ages.

Q: If an OT patient has a family member with Essential Tremor (ET) is there a genetic relationship?

A: ET is found in 10% of the general population; OT is one in 100,000 to 1,000,000.

Q: Some OT patients have had 23 and Me Genetic Testing. Would seeing this kind of testing for all OT patients be helpful?

A: Yes, but we cannot obtain this without permission. We will look at it in the future.

Q: Is OT progressive or not?

A: How long have you had it? Patients who have had OT for 20-30 years generally see worse symptoms.

Q: What % of this Phase III study had MRIs?

A: 24 out of 52

Q: Can we get copies of our test results?

A: Yes, in about 2-4 weeks, you may email and ask for them.

Peggy spoke briefly and acknowledged that without Gloria and Jeff, we would not be here participating in this study, and she presented Dr. Torres with a plaque of recognition. Peggy also read a card from Jeff thanking people for donations made in his honor to the OT Fund at UNMC and also thanking his mother, Gloria, for providing a forum on the website so that we could organize our search for more

information and provide a support for people who have OT. The absence of Gloria, Jeff and Beth were definitely missed at this event.

Sixteen raffle items were drawn ranging from a full-size hand-made quilt to gift certificates, a fruit basket and decorative glass plate, raising \$1,675. to be added to the Fund for Orthostatic Tremor Research and Education at the University of Nebraska Foundation.

Over \$35,000 has been raised for the UNMC OT Research Fund as of September 1 and Dr. Torres was awarded an additional grant for this Phase III study. 24 fMRIs cost over \$20,000. 30 Ophthalmology exams \$1757; 71 EMG exams over \$28,000. All testing by clinicians and assistants was performed gratis and with costs deferred to participating departments.

Treatment of OT by Dr. Danish Bhatti

How do we treat OT now?

- We think of it as a tremor disorder.
- If we can stop the tremors, everything will be fine.
- Is there evidence-based treatment?
- Clonazepam offers some relief to 2 out of 3 patients but there have been no randomized clinical trials. Of 100 patients 30% had a response but it was not long-lasting and some experienced a worsening of ataxia (clumsiness.)
- Only two drugs have been studied in clinical trials.
 - Gabapentin.
 - Levatriacetam (no benefit).
- Many tremor drugs have been reported as effective in individual patients.
- There has been some limited use of Deep Brain Stimulation which has also helped Essential Tremor.
- Not all OT is the same:
 - Pure OT
 - OT with AT (Action Tremor)
 - OT Plus (with other movement disorders)
- There are differences in patients and their individual responses to clonazepam.
- Levadopa is more effective in patients who also have Parkinson's Disease.
- Alcohol works for some patients.
- BOTOX helped one patient.

What is OT?

- Is it a tremor, unsteadiness or phobia? (Most OT patients never fall).
- Would it help to wear tremor cancellation devices (gloves, stockings etc.)?

Dr. Torres: Updates on the UNMC Research Program

Q: What are the long-term effects of maximum dose Clonazepam?

A: Prolonged use can increase ataxia; can create a drug-induced problem that might not be reversible. Can induce some brain cell loss.

Q: Any tests on the use of marijuana?

A: Worth looking into this. There are no known mechanisms that can help.

Q: Spinal cord stimulation?

A: Not enough information yet. Trying to set up an international study on Spinal Cord Stimulation

Q: Long term effects of Gabapentin?

A: Less than Clonazepam. The side effects are reversible when Gabapentin is stopped.

Q: If alcohol helps, is there a pill for the same effect?

A: No. 80% of patients who respond to alcohol had a temporary reduction of tremor. A pill was developed but it failed. If you are using Clonazepam and it's working, don't stop. Don't take another medication that might not work.

All OT patients have ataxia.

Updates on UNMC Study Status:

- We began working on OT in 2009.
- Completed projects: OT App developed in 2014, accepted in 2017.
- OT screening questionnaire offers 100% certainty for diagnosis of OT or not OT.
- OT Psych Study
 - Tremor is real.
 - This is not a psychiatric illness.
 - Video Magnification increases the ability of doctors who are not OT experts to diagnose OT patients.

OT Questions Remaining

- Do we really know what OT is?
- Why don't OT patients fall more often?
- Where in the brain does OT originate?
- Can OT teach us how to prevent falls in other movement disorders?
- What are the risk factors for getting OT?
- Can we cure OT?
- Why more women than men?
- Does OT affect quality of life and by how much?
- Since patients rarely fall, are OT patients truly unsteady or do they just feel unsteady?
- How can unsteadiness cause tremor? Is it the same tremor as when someone is frightened?
- What is the localization of the sensation of unsteadiness?

Future Directions?

- Work in progress
 - Biomechanics.
 - Virtual Reality Studies.
 - Delphi OT Project will help separate patients sensitive to fear from those who are not.

- ABC Scale of Fear of Falling
 - Anxiety and vestibular function.
 - Anxiety and postural centers.
 - Anxiety as a normal response.
- The threat doesn't matter. It's who's looking at it and how your brain has grown to respond to a particular response.
- Stress response is directly related to postural control and ambulation.
- Threat assessment: postural control and locomotion are integrated.
- Phobias respond to Clonazepam.
- Some common balance scales are abnormal in OT, but not all of them.
- Where is the oscillation? If it were spinal, the problem would only be in the legs.
- Tremor is found everywhere in OT patients including the head muscles.
- Tremor is synchronous in limbs, trunk and face.
- Is the problem between the brain stem and spinal cord?
- fMRI tests should give us a better understanding.
- We have completed 12 or so individual projects.
- There are about 40 ongoing projects from this week.
- From 2012 and 2014 there are three more projects to analyze.

Future Projects

- World wide on-line survey.
- Clinical Trials with oral meds.
- DBS (deep brain stimulation) trials.
- Spinal stimulation trials.
- TMS clinical trials.
- Genetics bank.
- CBT (Cognitive Behavior Therapy) Trials.
- Balance Training Trials.
- Core Strengthening Trials.
- Phobia Exposure & Propanolol Study.
- Base Phobia Evaluation.

3,770 pages of data collected the first day of this week-long event!

PRESENTATIONS HELD AT THE HOTEL BY OT PEOPLE

A presentation to a small group at the Element Hotel by RN Annetta Muir described her experimental treatment with spinal stimulation. An exterior spinal stimulation device worn for a week enabled her to stand for 5 minutes rather than the 20 seconds she was able to stand without the stimulator. Plans were made to implant this device but insurance refused to cover the costs, citing that spinal stimulation was approved for pain management only. See full presentation posted separately under the forum by searching under "spinal cord stimulation".

Elizabeth Copeland also gave a presentation on her experience in the Florida Clinical trials that took place earlier this year. More information is available on the forum by searching under "Florida Clinical trials".

Dr. John Bertoni of UNMC approached our group and asked if we would take part in a study he would like to do that would not be part of the research. He would like to get feedback on three questions that may help future people diagnosed with OT. Annetta Muir offered to take charge of this study and all OT people have been or will be contacted about filling out this form. Caregivers of OT people are also being asked to participate. If people would like to participate and have not been contacted they can contact Annetta - annettatn@aol.com. Deadline to send this in is November 1/17.

To sum up – this was an extremely successful meeting between our OT community participating and the wonderful professionals at the University of Nebraska Medical Center. We are so fortunate to have this partnership that I am sure will continue into the future.