Late Breaking News
Medications for Ataxia
Sunday, March 17th 10am

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PRESENTER DISCLOSURES

- Susan L. Perlman, M.D.
- The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

  Dr. Perlman has received research funding from Edison Pharmaceuticals Inc.
  
  Dr. Perlman is receiving research funding from the Friedreich’s Ataxia Research Alliance, the National Ataxia Foundation, and the National Institutes of Health.
Basic and Clinical Research in Ataxia--
PubMed

- 30,540 publications dealing with ataxia going back to 1879
- 374 in the past 3 months
- 18 dealing with humans—mostly recessive ataxias

- 9377 publications dealing with ataxia treatment going back to 1882
- 7 in the past 3 months pertaining to humans—
  1 addressing B12 deficiency
  6 addressing drug treatments that cause ataxia
1993—triplet repeat brain disorders described

Exponential growth is often used to describe surprisingly fast growth, such as in:

• the growth of microorganisms in a culture
• the effect of compound interest on investments
• nuclear chain reactions
• internet traffic growth
• human population growth.
Clinical Trials in Ataxia—ClinicalTrials.gov

108 studies listed
77 interventional

21 open
- Erythropoetin, EPI–743, and B3 in FA; Deferiprone in Parkinson's disease
- IVIG in SCA3
- Memantine in FXTAS
- Mesenchymal stem cells
- Riluzole
- Dalfampridine
- Immune therapies in paraneoplastic ataxia
Current and Emerging Research Directions
Not Yet Presented

We have already heard about:

- Exome sequencing and the search for new ataxia genes
- How ataxia genes cause ataxia—Friedreichs; SCA 2, 3, 5, 7, 8
- The function of the cerebellum, including in cognition/emotion
- New drugs to treat symptoms, the genetic cause, or restore nerve cells
- Induced pluripotent stem cells
- Non-drug treatments for ataxia—physical therapy, speech & swallowing therapy, sensory augmentation, balance vest, yoga
- Predicting and managing the progression of ataxia
- And we will hear about immune/inflammatory causes of ataxia, specifically gluten ataxia
- (But, not much else has been said about sporadic ataxia)
So What Hasn’t Yet Been Presented?

65th Annual Meeting of the American Academy of Neurology in San Diego this week

- 125 abstracts for posters and presentations about ataxia or imbalance
- Eg. Adapted Tango Dancing for Parkinson's Disease (PD) Can Be Safely Delivered in Community-Based Settings
- Rare recessive ataxias; FA; SCA 2, 3, 10, 31, 36; mitochondrial ataxias
- Acquired ataxias—toxic, immune-mediated; paraneoplastic
- Better rating scales to monitor ataxia—cerebellar ataxia, FXTAS, MSA
- Drug trials—

  Resveratrol in FA, Lithium in SCA2 and 3, Memantine in FXTAS, IVIG in immune-mediated ataxia, Rifampicin in MSA
An Open Label Clinical Pilot Study of Resveratrol as a Treatment for Friedreich-Ataxia
Martin Delatycki’s group in Australia

• 27 participants were enrolled in this open-label sequential clinical pilot study. Thirteen participants received resveratrol 1g daily (low-dose), and fourteen received resveratrol 5g daily (high-dose).

• Preliminary analysis of results from this open-label trial suggests that treatment with high-dose resveratrol for 12 weeks improves some clinical and biological markers of FRDA. GI side effects were seen.

• A placebo-controlled study is required to assess whether resveratrol is clinically beneficial in FRDA.
Lithium—disease modifying for SCA?

- **A Pilot, Randomized, Placebo-Controlled, Trial of Lithium in SCA 2**  Francesco Sacca et al.
  
  9 of 17 received lithium at therapeutic dose for 48 weeks
  
  Lithium was well tolerated and reported AEs were similar to those previously described for bipolar disorder patients. Although not significant, secondary endpoints are in favor of the lithium group. A correctly powered phase III trial is needed to assess if lithium may slow disease progression in SCA2.
  
  (Similar to results seen in the lithium trial for SCA1.)

  
  31 of 62 received lithium at therapeutic dose for 48 weeks
  
  This study provides Class 1 evidence that Lithium is safe in SCA3/MJD. 50% of subjects had side effects. Interim
Effects of Memantine on Language–Related Potentials in Patients with Fragile X–Associated Tremor/Ataxia Syndrome (FXTAS)
Randi Hagerman’s group at UC Davis

• Memantine, an N–methyl–D–aspartate (NMDA) receptor non–competitive antagonist approved for Alzheimer's disease, might help block glutamate–associated excitotoxicity and/or facilitate glutamatergic–signaling in FXTAS.

• Memantine therapy of 1 year duration in FXTAS was associated with an improvement in a language–related brain potential (EEG), specifically the early portion of the N400 became more sensitive to word repetition. The increased early N400 repetition effects suggest facilitation of implicit memory and automatic semantic activation processes.
IVIG

- **Autoimmune–Mediated Cerebellar Ataxia: Observation of Clinical Response to Intravenous Immunoglobulin** N Herial et al.

- **Intravenous immunoglobulin (IVIG)** has been used in treating many autoimmune–mediated neurological disorders. However, there are no current guidelines for clinical use of IVIG in treating cerebellar ataxia and the reported clinical response is varied.

- **Case report**—autoimmune–related due to the presence of anti–thyroid peroxidase antibodies; Periodic IVIG treatments yielded consistent clinical improvement in symptoms and cerebellar signs, as noted in physical examinations and repeat VNG (vestibulonystagmogram).

- **Autoimmune–mediated cerebellar ataxia** may be related to thyroid disease in the presence of autoantibodies. Immune–modulating treatments such as IVIG can be effective. VNG appears to be valuable
Efficacy of Oral Rifampicin in Multiple System Atrophy
Masaki Ohyagi et al.

24 subjects taking 450mg of Rifampicin every morning for 6 months

Data analysis still underway, but

It is possible that rifampicin helps to delay the progression of MSA. Larger numbers of patients with a sufficient number of controls are necessary to evaluate the effectiveness of rifampicin

- The US Mayo Clinic/Vanderbilt U study of 100 subjects (50 on drug, 50 on placebo) has finished and data analysis is still underway, but preliminary data suggests no therapeutic effect of drug compared to placebo
Sporadic Ataxia?

Much of the work going on now is focused on —

- Inflammatory/immune mechanisms
- Genetic risk factors for environmental exposures
- New ataxia genes (is everything really genetic?)
UCLA ATAXIA CENTER DEMOGRAPHICS
1562 PATIENTS SEEN BETWEEN 1995 AND 2005 (CURRENTLY BEING UPDATED)
ONLY 515 WERE FOUND TO HAVE AN IDENTIFIABLE CAUSE

GENETIC (Total 656, 45% identified)
Dominant (329)
Known mutation  196
Unknown mutation  129

Recessive (250)
Known mutation  149
Unknown mutation  101

X-linked or Mitochondrial (80)
Known mutation  18
Unknown mutation  62

SPORADIC (Total 904, 17% identified)
Known acquired cause  152
Combined cortical atrophy  14
HSA/HSP  76
MSA  72
PSP  20
Pure cerebellar  219
SOPCA  97
With unusual features  254
(dementia, diabetes insipidus, dizziness, vertigo, episodic features, dystonia, myoclonus, neuropathy, spasticity, tremor, white matter changes)
Approach to the Late-Onset, Predominantly Cerebellar Syndromes

Assign a phenotype by H & P, imaging, electrodiagnostics, LP

Obtain a detailed family and environmental history

Rule out known acquired causes.

Consider genetic testing—

Screening for FXTAS, SCA6, FRDA, as well as SCA1,2, and 3 will identify over 50% of possible inherited causes and cost less than $3000.

2–5% of sporadic cases turn out to be genetic
Everyone Deserves a Screen For

Neural localization (MRI, ENG, EPs, EMG/NCV)
Acquired factors—prior illnesses, toxic exposures or medication (Dilantin, amiodorone, chemotherapy)
Other medical problems—
thyroid dysfunction
low B12 or E
syphilis, EBV, Lyme, HTLV1, HIV
rheumatologic
factors
Immune/paraneoplastic—
Is This Pure Cerebellar or an Early Multiple System

80% of MSAs start with Parkinson’s symptoms
20% of MSAs start with cerebellar ataxia
25% of patients with sporadic cerebellar ataxia will go on to develop MSA (non-levodopa responsive Parkinsonism, autonomic dysfunction) within 5 years, especially if they are between the ages of 50 and 70
Erectile dysfunction can precede ataxia by 5–10 years
Notable cerebellar disability is seen often within 2–3 years
Sleep behavioral disturbances, obstructive sleep apnea,
So What Do We Have Now?
Common Medication Strategies for Treating

- There are no FDA approved drug treatments for Ataxia
- Not for symptoms, disease modification, or neural restoration

- There are a lot of medications used off-label to treat symptoms
- There are many published articles looking at these medications
  (see your handout for a list of drugs studied and used in ataxia)
- The physician and patient have to weigh risks vs. benefits

- If your doctor can’t advise you in this, seek guidance from an ataxia specialist
  (NAF has a list of ataxia specialists across the US)
There’s the Internet

http://www.neuro.wustl.edu/neuromuscular
http://www.geneclinics.org
http://www.curefa.org
http://www.ataxia.org
http://www.clinicaltrials.gov
And there’s the Internet
“They couldn’t put it on the Internet if it wasn’t

Search “cure ataxia”—

“Below are Natural Cures For Ataxia related alternative medicine supplements and vitamins. Also explore information on treatment, health benefits & side effects with Natural Cures For Ataxia products. Many of the sources come from our Encyclopedia of Natural Health and include relevant health topics. Uses vary, but may include Increasing Energy, and Relieving Sore Throat and are non–FDA reviewed or approved, natural alternatives, to use for Osteoporosis, and Anxiety. Natural Cures For Ataxia products are reviewed below. “

Or
http://hopestemcell.com/stem-cell-treatments/ataxia

And many others like this—doing “research” at your expense.
Drugs For Ataxia
These are all off-label, but modestly supported by published studies. There may be more.

**Amantadine,**

**Buspirone**

**Varenicline** (Chantix)

**Riluzole**

Common side effects may include dizziness and sleepiness.

**Fluoxetine** (speech, swallowing)

**L-5-hydroxytryptophan**

**Memantine**

**Physostigmine**

**Tandospirone**

**Thyrotropin releasing factor**

**Meclizine, Scopolamine, Ondansetron** (vertigo)

**Acetazolamide, Dilantin, Flunarizine** (episodic ataxia)
For tremor, myoclonus, nystagmus—

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<thead>
<tr>
<th>4-aminopyridine</th>
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<td>Baclofen</td>
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<td>Isoniazid</td>
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Botulinum toxin shots

Surgery, stimulators
Drugs For Fatigue
Better energy will improve performance

Pyridostigmine
Amantadine
Selegiline
Methyphenidate
Modafinil, Armodafinil
Fluoxetine
Caffeine (Monster drinks?)
Creatine, L-Carnitine
Anti-oxidant vitamins, B12

Non-drug approaches as well--
Look for other illnesses, drug side effects
Good nutrition.
Conditioning exercise.
Weight management.
Pain control.
Sleep hygiene.
Energy conservation.
Lifestyle modification.
Emotional health.
Alternative or Complementary Therapies
Testimonials do not substitute for evidence-based scientific research

Examples and classes of alternative treatments

1. Ayurvedic medicine
2. Traditional Chinese Medicine
3. Homeopathy
4. Naturopathy
5. Energy Therapies
   Biofields
   Electromagnetic Fields
6. Mind Body Therapies
7. Herbs, Diet and Vitamins
8. Body manipulation
Stanford Hopes Website

Abnormalities in energy metabolism
- Coenzyme Q-10
- Carnitine
- Riboflavin
- Nicotinamide
- Creatine

Free radical damage
- Arginine
- Vitamin E
- Vitamin C
- Lipoic Acid
- Selenium
- Gingko Biloba

Inflammation
- Folic Acid
- Minocycline
- Omega-3 Fatty Acids
- NSAIDs
- Glucocorticoids

Glutamate Toxicity
- Memantine
- Lamotrigine
- Lithium
- Riluzole
Quinones—coQ10

CoQ10 plays a unique role in the electron transport chain (ETC). In the inner mitochondrial membrane, CoQ10 functions as an electron carrier from enzyme complex I and enzyme complex II to complex III in this process. This is crucial in the process, since no other molecule can perform this function. Thus, CoQ10 functions in every cell of the body to synthesize energy.

The antioxidant nature of CoQ10 derives from its energy carrier function. As it accepts electrons, it becomes reduced. As it easily gives up electrons, it becomes oxidized and something else becomes reduced. Hence, coQ10 acts as an anti-oxidant.

A daily dosage up to 3600 mg was found to be tolerated by healthy as well as unhealthy persons. However, some adverse effects, largely gastrointestinal, are reported with very high intakes. The observed safe level (OSL) risk assessment method indicated that the evidence of safety is strong at intakes up to 1200 mg/day, and this level is identified as the OSL.

Statins can reduce serum levels of coenzyme Q10 by up to 40%. Some research suggests the logical option of supplementation with coenzyme Q10.
Does CoQ10 help protect the brain in ataxia?


Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up.


Coenzyme Q(10) (400 mg/d) and vitamin E (2100 IU/d) in 10 patients with FA over 47 months.

There was a significant improvement in cardiac and skeletal muscle bioenergetics that was maintained throughout the 47 months of therapy. Echocardiographic data revealed significantly increased fractional shortening at the 35– and 47–month time points. Comparison with cross-sectional data from 77 untreated patients with FA indicated the changes in total International Cooperative Ataxia Rating Scale and kinetic scores over the trial period were better than predicted for 7 of the 10 patients, but the posture and gait and hand dexterity scores progressed as predicted.

CONCLUSION:

This therapy resulted in sustained improvement in mitochondrial energy synthesis that was associated with a slowing of the progression of certain clinical features and a significant improvement in cardiac function.
• There is some evidence that coQ10 can be beneficial in other mitochondrial ataxias.

• CoQ10 is beneficial in conditions with coQ10 deficiency. In other neurogenetic disorders? It may depend on the role of the mitochondrion.


Coenzyme Q10, at 600mg per day, did not produce significant slowing in functional decline in early HD.

Cf. that Coenzyme Q10 was safe and well tolerated at dosages of up to 1200 mg/d and less disability developed in subjects with Parkinsons disease, assigned to coenzyme Q10 than in those assigned to placebo. Coenzyme Q10 appeared to slow the progressive deterioration of function in PD.
Medical Marijuana

A little science thanks to Wikipedia—

Cannabis contains 483 compounds. At least 80 of these are **cannabinoids**, which are the basis for medical and scientific use of cannabis.

Cannabinoids can serve as **appetite stimulants**, **antiemetics**, **antispasmodics**, and have some **analgesic** effects. Six important cannabinoids found in the cannabis plant are tetrahydrocannabinol (THC) and others.

In 1990 the discovery of **cannabinoid receptors** (CB1 and CB2) located throughout the **brain** and body, along with **endogenous** cannabinoid **neurotransmitters** like **anandamide**, suggested that the use of cannabis affects the brain in the same manner as a naturally occurring brain chemical.
Cannabis have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases.

The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Research is ongoing.
Acute effects while under the influence can include euphoria and anxiety.

Concerns have been raised about the potential for long-term cannabis consumption to increase risk for schizophrenia, bipolar disorders, and major depression, but the ultimate conclusions on these factors are disputed.

The evidence of long-term effects on memory is preliminary and hindered by confounding factors.

The THC molecule, and related compounds, are usually detectable in drug tests from 3 days up to 10 days; heavy users can produce positive tests for up to 3 months after ceasing cannabis use.
Marinol

(Dronabinol is a cannabinoid designated chemically as (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol.)

Approved 1985 in the USA (1992 in Canada)

For nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments

Approved 1992 in the USA

For anorexia associated with AIDS–related weight loss

Cost **US $ 652** for 30 doses @ 10 mg online
Since the medical marijuana movement began, twenty states and the District of Columbia, starting with California in 1996, have legalized medical cannabis or effectively decriminalized it—at the state level (Marijuana is still illegal in the eyes of the federal government, which overrules states' rights.)

Alaska, Arizona, California, Colorado, Connecticut, Delaware, Hawaii, Maine, Massachusetts, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, Virginia, Washington; and Washington D.C.

In November 2012, voters in Washington and Colorado passed ballot initiatives to legalize marijuana for recreational use.

The NAF annual membership meeting in Denver in two years should be very interesting.
EXERCISE ALWAYS HELPS ATAXIA
BRAIN AEROBICS
You Need to Have Your Questions Answered
NAF and its network of ataxia specialists can help

WHAT DO I HAVE?
WHAT IS THE CAUSE?
ARE MY CHILDREN AT RISK?
WILL IT GET WORSE?
HOW BAD WILL IT GET? HOW SOON?
CAN IT BE TREATED?
CAN IT BE CURED?
IS THERE ANY RESEARCH BEING DONE?
HOW CAN I GET ACCESS TO DIAGNOSTIC TESTING AND TREATMENT?
Partners in Clinical Neurogenetics Research at UCLA

Daniel Geschwind, M.D., Ph.D., Neurogenetics Program Director (Molecular Genetics, DNA bank)
Susan Perlman, M.D., Ataxia Clinic Director (Ataxia Database, Drug Trials)
Brent Fogel, M.D., Ph.D. (Molecular Genetics, DNA bank)
Robert Baloh, M.D. (Neuro-Otology)
George Bartzokis, M.D. (Neuroimaging, Biomarkers)
Yvette Bordelon, M.D., Ph.D. (Huntington’s disease, Biomarkers, Drug Trials)
Stephen Cederbaum, M.D. (Medical Genetics, Metabolic Disorders)
Giovanni Coppola, M.D. (Molecular Genetics)
Ming Guo, M.D., Ph.D. (Drosophila)
Michelle Hamilton, M.D., Juan Alejos, M.D. (Cardiology)
Joanna Jen, M.D., Ph.D. (Episodic Ataxias, Drug Trials)
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THANK YOU

National Ataxia Foundation—
sponsor of grants for our internal database, our DNA bank, and our web-based database project.

Muscular Dystrophy Association and
Friedreich’s Ataxia Research Alliance—
sponsors of the grant for the collaborative project on “Clinical Outcome Measures in Friedreich’s Ataxia”.

The Smith Family Foundation; The Lapin Family Fund; The Bettencourt Fund

And to our patients and their families
for their willingness to work with us and to share with us their ideas and hopes.