Welcome
Overview of FA Symptoms and Management

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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 is receiving research funding from Edison Pharmaceuticals, ViroPharma/Shire, Horizon Pharmaceuticals, Teva Pharmaceuticals, Pfizer Pharmaceuticals.

Dr. Perlman is receiving research funding from the Friedreich’s Ataxia Research Alliance, the National Ataxia Foundation, and the National Institutes of Health.

1/21/2016
As Patients and Families with FA

• You must support each other.
• You must educate each other and your communities.
• You must educate your healthcare providers.

• The best resources to do this:
  FARA’s website (research pipeline, clinical care guidelines)
  FAPG listserve and other social media (?concerns)
  Clinicaltrials.gov
  And other online medical sites for the lay public.

However: I still have patients and families asking me if they should go to Mexico for stem cells.....
Raw Food Detox Diet * Natural Healing from Friedreich's Ataxia ❤

liferegenerator

- Uploaded on Jul 25, 2009 to YouTUBE
- http://SHOP.life-regenerator.com *CLICK HERE FOR NOTES! The child of a friend of mine is ataxic, from a neurological condition called Friedreich's Ataxia, and they asked me what I would do, if my own child had the same condition. ❤

- 56 comments posted.
- Many along the lines of: As a health professional, it is important to 'think out of the box' and look at natural ways and healing foods to assist the body to assist itself as well as medical research.
- Some: So... If I have FA and I eat raw food and herbs, I'll become "normal" again and won't have FA anymore?
- But the best comment:
  I have to tell you mate, this video is utter bollocks. I am a gluten free vegan and FAer. I am not vegan because of FA. This is completely inappropriate and unethical advice to be giving. I hope that people watching this video will not take it seriously. You do not understand FA after researching it online for ten minutes.
Overview of FA Symptoms

http://neuromuscular.wustl.edu/ataxia/recatax.html#FA
(this is rather like preaching to the choir)

• Like most mitochondrial diseases, FA has neurologic and non-neurologic symptoms

  – Neurological features
    • Cerebellar (100%)
      – Ataxia: Limb & Trunk; Gait (100%)
      – Ocular: Square wave jerks (Common); Nystagmus (20%)
      – Dysarthria (95%): Onset within few years
      – Dysphagia: Late in disease course; Liquids
      – Course: Progressive with increasing age
    • Sensory loss (~80%)
      – Vibration & Joint position: Prominent loss
      – Light touch & Pin: Also reduced
    • Autonomic
      – Cold, cyanotic uncomfortable legs & feet: Late in course
      – Sphincters normal

  • Motor
    – Weakness (67% to 88%)
      » Lower extremities
      » May be in "pyramidal" distribution
    – Muscle wasting: Small muscles in hands & feet
  • Tendon reflexes: Absent (75%) or reduced
  • Corticospinal tract signs
    – Extensor plantar responses (80%)
    – Spasticity: Intermediate number of repeats
  • Optic atrophy (30%): May be no visual impairment
  • Chorea: Occasional patient may have chorea without ataxia
  • Hearing loss: Sensorineural (20%)
  • Cognitive: Mostly preserved
• Cardiac (50% to 75%)
  ▪ Clinical
    ▪ Often asymptomatic
    ▪ More common with: Earlier age of onset
    ▪ Early symptoms: Shortness of breath; Palpitations
  ▪ Hypertrophic cardiomyopathy
    ▪ EKG: T-wave inversions
  ▪ Muscular subaortic stenosis
  ▪ Hypokinetic-dilated left ventricle
    ▪ Q waves; Poor prognosis
  ▪ EKG: Abnormal (65%)
  ▪ Echocardiography
    ▪ Concentric hypertrophy of ventricles
    ▪ Asymmetric septal hypertrophy
  ▪ Treatment
    ▪ Idebenone 5-10 mg/kg/day at onset of hypertrophic cardiomyopathy
  ▪ Severity: Variable; May be minimal or cause of death

• Systemic Features
  • Skeletal
    ▪ Scoliosis (60% to 80%)
    ▪ Pes cavus or equinovarus (50% to 75%)
  • Endocrine
    ▪ Diabetes mellitus (10%): Especially with FA onset < 10 years
    ▪ Carbohydrate intolerance (20%)
      ▪ β-cell dysfunction
      ▪ Peripheral insulin resistance
  • Sphincter disturbance (~25%)
  • Anesthesia: ? Avoid depolarizing NM blocking agents

1/21/2016
FARA UCLA Friedreichs Ataxia Patient Symposium
Friedreich ataxia: Variant neurological syndromes

- Late onset Friedreich ataxia syndrome (LOFA)
  - Genetics
    - Frataxin: Shorter GAA expansion on smaller allele
  - Clinical
    - Onset: May be as late as 50 to 70 years
    - All patients
      - Ataxia: Gait & Limb
    - Some late onset patients
      - Normal reflexes
      - Predominantly spastic paraparesis or tetraparesis
    - Less frequent
      - Dysarthria
      - Skeletal deformities
      - Absent reflexes
      - Scoliosis
      - Cardiomyopathy
  - Course: Slower progression
    - MRI: Cerebellar atrophy in 50%
  - Spastic ataxia: 2 molecular associations
    - Intermediate number of GAA repeats (120-156): Onset 38 to 45 yrs; Acadians
    - Missense mutations in amino-terminal half of FRDA (Frataxin) in one allele
  - Friedreich ataxia with retained tendon reflexes
    - Otherwise typical FA clinical syndrome

- Early onset with rapid progression
  - Mutations
    - One allele
      - Missense mutation in carboxy half of FRDA: Exon 5a; R165P
    - 2nd allele: Typical GAA expansion
  - Clinical syndrome
    - Early onset: Gait ataxia; 1st decade
    - Cerebellar
      - Gait disorder
      - Dysmetria: Upper limb; Mild
      - Dysarthria: Absent or very mild
    - Upper motor neuron
      - Weakness in lower extremities
      - Upgoing toes
    - Tendon reflexes: Arms normal; Some retained knee jerks
    - Peripheral nerve involvement: Slight to moderate; Sensory potentials present
    - Diabetes
    - Skeletal: Pes cavus
  - Disease progression: Rapid; Wheelchair in 2nd decade
Acadian Type (Louisiana Form)
- Epidemiology: French origin living in North America
- Frataxin mutations: Intermediate number of repeats
- Milder course
- Lower incidence of cardiomyopathy

FRDA2
- Epidemiology: 3 consanguinous families
- Genetics: 9p23-p11 linkage; Not linked to frataxin gene
- Clinical features: Similar to FRDA with frataxin gene mutations
  - Onset age: 5 to 14 years
  - Ataxia: Progressive
  - Sensory: Loss, especially vibration & Joint position
  - Tendon reflexes: Absent or Reduced

Work just begun, looking at other associated symptoms:
- Friedreich Ataxia and nephrotic syndrome: a series of two patients.
  - Shinnick JE1, Isaacs CJ2, Vivaldi S3, Schadt K4, Lynch DR5,6.
- ?Other autoimmune disorders, steroid responsiveness

- Friedreich ataxia clinical outcome measures: natural history evaluation in 410 participants.
  - Regner SR1, Wilcox NS, Friedman LS, Seyer LA, Schadt KA, Brigatti KW, Perlman S, Delatycki M, Wilmot GR, Gomez CM, Bushara KO, Mathews KD, Subramony SH, Ashizawa T, Ravina B, Brocht A, Farmer JM, Lynch DR.

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Abstract
- Friedreich ataxia is an autosomal recessive neurodegenerative disorder characterized by ataxia, dysarthria, and areflexia. The authors report the progress of a large international noninterventional cohort (n = 410), tracking the natural history of disease progression using the neurologic examination-based Friedreich Ataxia Rating Scale. The authors analyzed the rate of progression with cross-sectional analysis and longitudinal analysis over a 2-year period. The Friedreich Ataxia Rating Scale captured disease progression when used at 1 and 2 years following initial evaluation, with a lower ratio of standard deviation of change to mean change over 2 years of evaluation. However, modeling of disease progression identified substantial ceiling effects in the Friedreich Ataxia Rating Scale, suggesting this measure is most useful in subjects before maximal deficit is approached.
In Friedreich’s Ataxia, change was most reliably seen over 1 to 2 years of follow up and in earlier stages.
Possible Explanations and Areas for Further Research

  - Striking intrafamilial phenotypic variability and spastic paraplegia in the presence of similar homozygous expansions of the FRDA1 gene.
  - **Badhwar A**, **Jansen A**, **Andermann F**, **Pandolfo M**, **Andermann E**.
  - Factors such as somatic mosaicism, repeat interruptions, modifying mutations and environmental factors must also be considered.

  - Limited somatic mosaicism for Friedreich's ataxia GAA triplet repeat expansions identified by small pool PCR in blood leukocytes.
  - **Hellenbroich Y**, **Schwinger E**, **Zühlke C**.
  - A confident prediction of the prognosis deduced from the repeat length is hardly possible for an individual FRDA patient.

  - Somatic mosaicism for Friedreich's ataxia GAA triplet repeat expansions in the central nervous system.
  - **Montermini L**, **Kish SJ**, **Jiralerspong S**, **Lamarche JB**, **Pandolfo M**.
  - Regional differences in repeat size could not account for the characteristic distribution of pathology in FRDA, which appears instead to be related to the pattern of frataxin expression.
Situations Where it is Worthwhile Testing for Friedreich’s Ataxia

• Any person with ataxia onset before the age of 25.
• Any ataxic person of any age with at least one of the following symptoms (even if there is another known genetic ataxia in the family—lightning does strike twice):
  ➢ ataxia progresses from legs to arms to speech
  ➢ eye movements show “fixation instability”
  ➢ associated loss of vibration sense or joint position sense
  ➢ associated peripheral neuropathy causing muscle atrophy and loss of sensation for sharpness, temperature, light touch
  ➢ loss of reflexes with upgoing toe sign
  ➢ associated vision loss, hearing loss, heart disease, diabetes, scoliosis, foot deformity
  ➢ brain MRI is normal, but spinal cord MRI shows atrophy
Symptoms not Usually Seen in Friedreich’s Ataxia

- These symptoms suggest that Friedreich’s is not the cause or not the only cause and that other conditions should be sought:
  - mental retardation or progressive loss of memory
  - severe emotional disturbances
  - paralysis of eye movements
  - peripheral neuropathy causing muscle atrophy and loss of sensation for sharpness, temperature, light touch, vibration, joint position sense, but patient doesn’t have ataxia
  - headaches
  - upper gastrointestinal complaints
  - frequent infections
  - skin problems

- Just because you have Friedreich’s ataxia, you are not immune to other health problems.
Symptoms not Usually Seen in Friedreich’s Ataxia in the First 10 Years

- In particularly severe forms of FA, these symptoms can be seen in the first 10 years, but in the average patient they present after 10 years if they present at all (sometimes they don’t):
  - vision loss
  - hearing loss
  - severe problems with speech and swallowing
  - trouble breathing due to muscle weakness in throat/chest
  - severe muscle weakness in arms and legs
  - bowel or bladder problems
  - sleep disturbances
  - If these are seen in the first 10 years of FA, other causes should be sought. Maybe it is the FA, but you have to look outside the box.
Everyone Deserves a Screen For

- Neural localization (MRI, ENG, EPs, EMG/NCV)
- Acquired factors—prior illnesses, toxic exposures or medication side effects
- Other medical problems—
  - thyroid dysfunction
  - low B12 or E
  - syphilis, EBV, Lyme, HTLV1, HIV
  - rheumatologic factors
- Immune/paraneoplastic—anti-GAD, anti-gliadin
  - anti-Yo, Ri, MaTa, CV2, Zic4, TR
- Another genetic disease, if the situation suggests
We still don’t fully understand what happens in Friedreich’s ataxia

• The CCRN-FA with FARA has worked aggressively to support clinical research in natural history, specific pathophysiology, molecular genetic actions, biomarkers, and drug development.

• Interdisciplinary and international collaboration has flourished.

• More and more investigators and private companies are becoming aware of FA and its unmet needs.
FA TREATMENT PIPELINE – JANUARY 2016
http://www.curefa.org/pipeline
While Back in around 2007.....
How FARA Supports Drug Development

- Patient Registry and recruitment to facilitate clinical trials
- CCRN (Clinical Trial Research Network and Trials)
- Biomarker Identification to facilitate Phase II Trials
- Ataxia Scales (end points) to facilitate Phase III Trials
- Translational Research
- Basic Research to keep filling pipeline
- Education and Awareness Initiatives (patients, physicians, healthcare providers)
- Enlist support from Government and Industry
- Relationships with patient and scientific communities as well as Patient Advocacy Groups in other diseases
OFFICIAL PIPELINE FOR NEW DRUGS

Up to 15 years and $500-700 million to get to market

- Discovery—clinicians and scientists working out the cause of the disease, the “dominos” that fall over, and targeted candidate drugs.
- Preclinical testing—test tube and animal studies.
- Phase I—dosing, safety
- Phase II—safety, possible efficacy
- Phase III—efficacy
- FDA Approval
- Phase IV—Post-marketing studies for long-term side-effects and good effects.

To help with promising drugs for serious diseases with unmet needs:
- NIH—Rapid Access to Intervention Development (RAID)
- FDA—Orphan Drug Status
DO WE REALLY NEED PLACEBOS?

• Gold Standard for Phase III clinical trials is the double-blind, placebo-controlled, randomized study.
• The “placebo effect” is very real and accounts for all the other effects not related to the drug directly.
• Dramatic differences between the placebo and drug groups will usually result in all subjects being placed on drug before the end of the trial.
• If it would be dangerous for a potential subject to end up on placebo, that subject would not be enrolled in the study. This includes the subject having to stop other medications to enter the study.
• Active placebos may be used.
• Use of historical controls or subject acting as own control may require a longer study to prove benefit of drug.
Every Ataxia Patient Must Participate in Clinical Trials

1. Registries will enable you to be found. These are rare diseases with very small numbers of patients who can participate. Every person counts.

2. Be knowledgeable about what makes a good clinical trial—don’t make bad investments.

3. Speak up about the roadblocks to participation. Become involved in planning the trials.

4. Be prepared to make sacrifices.
Roadblocks for Patients
Must be prepared to make sacrifices

• Time
• Money
• Confidentiality
• Ultimately, choosing and giving up one drug trial for another.
Every Researcher Designing A Clinical Trial Must Make It Accessible To All Ataxia Patients.

• Design trials that can use the fewest patients over the shortest period of time (this usually means testing better drugs and using biomarkers).
• What is the rationale for excluding certain patients? Can those excluded be used in other ways? Parallel or compassionate studies?
But remember that a patient can participate in only one trial at a time and that participation in some trials may permanently disqualify participation in others.
• Reimbursing travel costs is essential for recruitment and compliance. Telemedicine?
• Don’t expect the patients to make unreasonable sacrifices.
Roadblocks for Clinical Researchers

• Picking the right drugs.
• Designing the trial properly—number of patients, measures/biomarkers, length of study, placebo, how many sites.
• Getting the FDA to agree.
• Getting funding.
• Finding sites and getting them approved.
• Finding subjects.
• Doing the work in a timely fashion.
Becoming A Knowledgeable Consumer

- General trial info:
  - Determining dosage maximum – is it safe?
  - How will my confidentiality be maintained? Identity disclosure issues
  - Explain need for exclusionary and placebo process
  - How to choose a trial and where to go
  - Telemedicine for trials?
  - Face to face presentation of each trial’s process/benefit and communicate to potential participants: Why do we have to discontinue our current meds? What are the measures of confidentiality required or available? Type of contact?

- In terms of ongoing trials:
  - Why is this trial being done?
  - What’s the long term benefit?
  - Explain what you’ll do in the trial—why will these measures show change?
  - Present info in clear format for FAQs, ex.: travel expenses, risks, disclosure
  - What are the side effects, benefits
  - How will participation affect or be affected by my current medications?
  - Concealment/placebo affects
UCLA Ataxia Center

• We have close to 200 Fa’ers registered in the Natural History Study. Some have been participating since the study’s start in 2002.
• We have participated in the Phase III Idebenone study, as well as the Phase III EPI-743 and the Phase I Ox-1 studies.
• I like to think of us as the West Coast anchor for the CCRN, headed by Dr. Lynch.
• But we need more sites West of the Mississippi.
We hand out this information to all our new patients and families

• 1. You may participate in the Friedreich's ataxia clinical outcome measures study annually.
• 2. You may give a blood sample to research for DNA and RNA analysis.
• 3. You may give a cheek swab sample to research for frataxin protein analysis.
• 4. Your parents may give a blood sample to research for RNA analysis.
• 5. Your parents may give a cheek swab sample to research for frataxin protein analysis.
• 6. You should see a cardiologist annually for a heart check (echocardiogram).
• 7. You should see an orthopedist annually for a spine and foot check.
• 8. You should have an annual blood test to screen for diabetes (fasting blood sugar or hemoglobin A1c; urine sugar test).
• 9. You should have a baseline vision and hearing test.
• 10. You should have an evaluation with physical therapy and occupational therapy about home exercise.
• 11. You should consider using an anti-oxidant supplement (vitamin E 400 IU each day, coenzyme Q10 400 mg each day OR Idebenone 500mg capsules three times per day with meals—available online at smartpowders.com).
• 12. Good resources for more information are--www.curefa.org (Friedreich's ataxia research alliance-FARA); FAPG list serve (Friedreich's ataxia parents group--contact Paul Konanz at pkonanz@comcast.net); and www.ataxia.org (National Ataxia Foundation).
• 13. Sign up in the Registry at www.curefa.org to receive notices about new research studies in which you can participate.
• 14. Rapidly changing symptoms are not your FA. Get them checked out.
MANAGEMENT OF FA

• Medication management of symptoms of ataxia
• Medication management of symptoms of spasticity
• Medication management of symptoms of peripheral neuropathy
• Skeletal, joint, or muscle pain
• Weight maintenance
• Bladder or bowel disturbance
• Disturbed sleep, fatigue
• Psychosocial difficulties
• Medical complications—diabetes, heart problems
• The importance of rehabilitation techniques
Symptoms of Ataxia

• Slurred speech, incoordination, imbalance, fatigue
• Tremor (may respond to typical tremor drugs)
• Dizziness and nystagmus (not typical problems in FA, but medications are available. Dizziness can be brought on by neck or ear problems).
• There are medications available that may reduce these symptoms and improve quality of life.
• All of these medications are used off-label.
• A detailed list has been provided to FAPG, which includes detailed side-effects.
• Ataxic symptoms may be made worse by weakness, increasing sensory loss, and fatigue or illness.
Medications for Symptoms of Ataxia

- Amantadine 100mg once or twice per day.
- Buspar 5-15mg twice per day.
- Amantadine can cause dry mouth and eyes, constipation, memory and mood changes.
- Buspar can cause spacey, dizzy feelings.
- Both of these medications have had several published open and controlled studies which showed variable efficacy.
- Two other tricks of the trade:
  - Low dose Prozac may prevent coughing and choking spasms.
  - N-acetylcysteine (available OTC) may help speech and tremor.
Symptoms of Spasticity

- Tightness of legs, trunk, arms that limit movement
- Involuntary spasms of legs, trunk, arms
- Painful spasms of legs, trunk, arms
- Tightness and decreased movement can lead to contractures at joints (joints no longer flex)
- Spasticity will worsen your balance and cause weakness.
- Drug treatment of spasticity can worsen your balance and cause weakness.
PYRAMID OF CARE
IN SPASTICITY MANAGEMENT

• Prevention of Nociception
• Physical Modalities: ROM, Static Stretching,
  Splinting, Serial Casting
• Oral Medications: Baclofen, Diazepam, Tizanidine,
  Clonidine, Dantrolene
• Intrathecal Baclofen Pump
• Permanent or Semi-permanent Options:
• Motor Point Blocks: Phenol, BOTOX®
• Nerve Blocks: Phenol
• Destructive Procedures: Neurectomy, Temnotomy,
  Myotomy
• Rhizotomy, Cordotomy, Myelotomy
Symptoms of Peripheral Neuropathy

- Muscle atrophy and weakness
- Numbness, tingling, burning, pain
- Loss of sense of where legs are
- The combination of weakness, that prevents easy change of position, and numbness, that prevents feeling uncomfortable pressure, can lead to pressure sores over pressure points.
- Loss of nerve supply to small blood vessels in skin can lead to cold, mottled, swollen legs.
- Immobility can increase the risk of blood clots.
Treatment of Peripheral Neuropathy

• Mobilize, to reduce weakness and swelling.
• If swelling of legs continues, elevate legs, use support hose, reduce salt.
• Review drugs that could contribute to swelling.
• Medications for neuropathy pain.
• Always try to treat any underlying cause.
Skeletal, Joint, or Muscle Pain

• May occur with progressive scoliosis or foot deformity.
• May occur with contractures.
• May be due to other conditions: arthritis, infection, fracture
costocondritis
ligament, tendon, or muscle sprain or strain
“growing pains” (Osgood-Schlatter syndrome)
referred from a neighboring joint or muscle
Treatment of Skeletal or Joint Pain

• Rule out serious causes of bone pain (arthritis, infection, fracture).
• Modify activities that increase pain.
• Relieve stress on skeleton or joint (bracing, strengthen muscles that support the joint).
• Medications for mechanical pain.
• Non-drug treatments
We are constantly surprised and challenged and encouraged

- The very first FAer I ever met was in 1979. He was in his late 20’s and had had a stroke due to a blood clot from his cardiomyopathy. That same year we lost a young FAer due to a stroke. The year before an older FAer had stroked out her kidneys.
Of the many advances made in the past almost 40 years, better treatment of the cardiomyopathy is the most lifesaving.

- Just the other day I was seeing a young man with an early onset ataxia (not FA). He mentioned his tremor got worse when he was anxious. I asked more about his anxiety (and depression). He shared that he thought about suicide every night—maybe taking all his pills at once.

We have to ask.
UCLA is excited to be participating in this current round of clinical trials

• STEADFAST: Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in FA—
  UCLA currently recruiting

• MOXle: RTA408 in FA
  UCLA will open for recruiting soon

• RT001: First in Human Study of RT001 in FA, Retrotope—UCLA will participate in next phase of this study later in 2016
Our Research Team

- March 2015
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)
- The George Bartzokis, M.D. Group (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)
- Arik Johnson, Psy.D. (Psychology)
- William Oppenheim, M.D. (Orthopedics)
- Noriko Salamon, M.D. (Neuroradiology)
- Ernest Wright D.Sc., Ph.D, Vladimir Kepe Ph.D., Jorge Barrio Ph.D. (Neuroimaging, Biomarkers)
- Brian Clemente Ph.D. — Ataxia Research Coordinator (310) 206-8153
- Nagmeh Dorrani, M.S. — Genetic Counselor (310) 206-6581
THANK YOU

• FARA and Horizon Pharma for their help in organizing this symposium.

• 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.
For Our Next Segment

• Clinical Trials Session – Moderator: Jen Farmer FARA Executive Director