NON-EXPERIMENTAL ISSUES OF DIAGNOSIS FOR FRIEDREICH'S ATAXIA

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DIAGNOSIS OF FA

- **If you are suspected of having a genetic ataxia, either by family history or type of symptoms, the only definitive test is a gene test. But not all genes can be tested at this time.**
- **1-5% of persons without a family history turn out to have a genetic cause for their ataxia (most of these have Friedreich's ataxia or SCA6).**
- **Sporadic ataxia is a diagnosis of exclusion.**
- **10% of conditions that look like Friedreich's prove not to be genetic FA.**
- **10% of conditions that don't look like FA prove to be genetic FA.**

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

- **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**

Symptoms not Usually Seen in Friedreich's 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**

Genetic Testing for Friedreich's

- **GAA expansions in the gene above 65 repeats reduce production of frataxin. This gene mutation is the one screened for by the gene test, which is done in many labs (www.geneclinics.org) and costs from $250-500.**
- **Unaffected at-risk children under the age of 18 may or may not be recommended for testing. When cures are available, everyone at-risk should be tested.**
- **In 4% of cases, a point mutation occurs in the gene that stops translation of RNA to frataxin or causes production of frataxin with reduced activity. Only a few labs screen for point mutations (in the US—Children's Hospital of Philadelphia and Horizon Medicine in Atlanta). This test costs 2-3x as much as the GAA test.**
- **If you look like you have FA, but the GAA test shows only one bad gene, it is reasonable to get the point mutation test done to look at the other gene.**
- **If both tests are normal, you could still have clinical FA, with something else interfering with frataxin activity, or you could have a different disease also affecting the pathway that frataxin acts in, or you could have a different disease affecting another pathway important for mitochondria or spinocerebellar nerves.**

FRDA PHENOTYPES—EXPANDING THE TERRITORY AND WE CANNOT ADEQUATELY EXPLAIN WHY

- **LATE-ONSET FRDA (LOFA)—15%** have onset between 25 and 51 years and possibly slower disease progression
- **FRDA WITH RETAINED REFLEXES (FARR)—12%** have retained or pathologically brisk DTRs
- **FRDA WITH SLOWLY PROGRESSIVE DISEASE—**seen in LOFA, the Acadian variant, and compound heterozygotes with certain missense mutations
- **FRDA WITH DEMYELINATING NEUROPATHY**
- **FRDA WITH PURE SENSORY ATAXIA**
- **FRDA WITH LATE-ONSET SPASTIC ATAXIA AND MINIMAL SENSORY CHANGES**
- **FRDA WITH CHOREA AND NO ATAXIA**
- **FRDA HETEROZYGOTES MAY (GERMAN STUDY) OR MAY NOT (DANISH AND DUTCH STUDIES) HAVE A HIGHER RISK OF NIDDM**

FRIEDREICH'S ATAXIA PHENOCOPIES

- **Ataxia with Vitamin E deficiency (8q13, α-tocopherol transfer protein/TTPA)—**
  slower course, no cardiomyopathy or diabetes, retinopathy in 1/3, head titubation, dystonia
  more common in North African and Mediterreanean populations
- **Abetalipoproteinemia (4q24, microsomal triglyceride transfer protein/MTP)—**
  retinopathy
  systemic features (fat malabsorption; acanthocytes; deficiencies of A, E, and K; low cholesterol, TG)
- **Refsum's disease (phytanoyl-CoA hydroxylase/PAHX or Peroxin 7/PEX7-late onset)—**
  retinopathy, neuropathy, deafness, myopathy, cardiomyopathy, ichthyosis
- **Cayman ataxia (19p13.3, Caytaxin/ATCAY)—**
  C-terminal domain binds vitamin E, similar to TTPA
  hypotonia, non-progressive ataxia, psychomotor retardation

- **Late-onset Tay-Sachs disease (LOTS, hexosaminidase A)—**
  spinocerebellar syndrome
  spinal muscular atrophy syndrome
  associated risk of psychiatric symptoms
  prevalent in Ashkenazi Jewish, French-Canadian, and Italian populations

- **Infantile onset spinocerebellar ataxia (IOSCA, 10q24.1)**
  athetoid movements, hypotonia, loss of deep tendon reflexes
  ophthalmoplegia, sensorineural hearing loss, optic atrophy, sensory neuropathy
  epilepsy
  so far found only in patients from Finland
- **Other single family syndromes are undergoing linkage studies (SCABD-6p21-23, chromosome 1)**

Early-Onset Cerebellar Ataxia with Retained Reflexes (EOCARR)

- No dominant pattern of inheritance
- Onset between 2 and 20 years of age
- Retained lower limb DTRs
- Sensory changes less commonly seen
- **Cerebellar atrophy on MRI**
- **Includes several distinctive syndromes--**
  - **Ataxia-telangiectasia**
  - **Ataxia-oculomotor apraxia 1 & 2**
  - **Complicated hereditary spastic paraplegias (e.g. ARSACS)**
  - **Late-onset inborn errors of metabolism**

Late-Onset Inborn Errors of Metabolism

- **Gray et.al., *JNNP* 2000 Jul 69:5-12.**
- **Ataxia—oxidative disorders**
  - **Wilson's disease**
  - **lysosomal storage (NP-C, MLD, Krabbe's)**
  - **late-onset Tay-Sachs, Sandhoff's sialidosis**
  - **Hartnup's disease**
  - **adrenomyeloneuropathy, Refsum's disease**
  - **vit E (AVED, a-/hypobetalipoproteinemias)**
  - **cerebrotendinous xanthomatosis**
  - **hemochromatosis**

Mitochondrial Syndromes

Maternal inheritance--no male to male transmission

- **Distinctive neurologic features**
  dementia, dystonia, exercise intolerance, hearing loss, migraine, myelopathy, myoclonus, myopathy, neuropathy, ophthalmoplegia, optic neuropathy, pigmentary retinopathy, seizures, stroke-like episodes
- **Distinctive non-neurologic features**
  adrenal dysfunction, anemia, cardiomyopathy, cataracts, diabetes mellitus, other endocrine dysfunction, exocrine pancreas dysfunction, intestinal pseudo-obstruction, lactic acidosis, renal disease, rhabdomyalysis, short stature