Non-Genetic Ataxia

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Is Anything Non-Genetic?

1,212,000 references in PubMed under "genetics"

- "In the 20th century, genetics progressed from the rediscovery of Mendel's Laws to the identification of nearly every Mendelian genetic disease. At this pace, the genetic component of all complex human diseases could be identified by the end of the 21st century, and rational therapies could be developed." (We should all live so long.)

- “...multiple mechanisms are involved in altering human phenotypes, including common alleles with small to moderate effects, rare alleles with moderate to large effects, complex gene-gene and gene-environment interactions, genomic alterations, and noninherited genetic effects.” Dean, M. (2003). Approaches to identify genes for complex human diseases: Lessons from Mendelian disorders. *Hum.Mutat*.22:261-74.

Neurologic Diseases with Genetic Aspects

- **One gene/one disease**
  (Mendelian)

  SCAs
  FRDA
  HSP
  Huntington disease
  Inborn errors
  PD 1, 3-5, 8 (AD)
  PD 2, 6-7 (AR)
  ALS
  Alzheimer's disease

- **Susceptibility genes**
  (one or more genes,
  plus other factors)

  Multiple sclerosis
  PD (5 genes)
  Alzheimer's disease
  Epilepsy
  Psychiatric illness
  Cancer
  Ataxia (?)
  MSA (?)

WHAT QUESTIONS DOES THE PATIENT ASK?

- **WHAT DO I HAVE?**
- **WHAT IS THE CAUSE?**
- **ARE MY CHILDREN AT RISK?**
- **CAN IT BE CURED?**
- **WILL IT GET WORSE?**
- **HOW BAD WILL IT GET? HOW SOON?**
- **IS THERE ANY RESEARCH BEING DONE?**

- **Currently the genetic ataxias hold the podium and offer the clearest answers for most of these questions. Many people are thinking genetics these days.**

I've had ataxia for 5 years, and my doctor has already sent for the gene testing, and it was normal. Now what can I do, Dr. Perlman?

- Athena Diagnostics, Inc.
  Four Biotech Park
  377 Plantation Street

  Worcester, MA 01605

10 ataxia gene tests and 2 HSP gene tests available, only about 50 to go

- **About 5% of patients without a family history will have one of the genetic ataxias.**
- **But 95% of patients without a family history will probably have non-genetic ataxia.**

Is This Genetic?

Any of these could present as sporadic conditions

- **Typical (or atypical) dominant cerebellar ataxia**
- **Friedreich's ataxia-like syndromes**
- **Early-onset cerebellar ataxia with retained reflexes**
- **Mitochondrial syndromes**
- **Multiple system atrophy picture**
  - **more rapid progression**
  - **non-L-dopa responsive Parkinsonism**
  - **autonomic dysfunction**
  - **REM sleep disturbance, sleep apnea, stridor**

Maybe I Have MSA?

- **There's been a lot published lately about MSA.**
- **North American MSA Study Group**

  Dr. Clifford Shults
  UCSD, Department of Neuroscience
  9500 Gilman Drive
  La Jolla, CA 92093
- **MSA starts like ataxia in 20%, like PD in 80%**
- **It progresses to include ataxia, Parkinsonism, and autonomic problems in everyone.**

Is This Pure Cerebellar Ataxia or an Early Multiple System Atrophy?

- **80% of MSAs start with Parkinsonian symptoms and 20% of MSAs start with cerebellar ataxia**
- **25% of patients with sporadic cerebellar ataxia will go on develop MSA (with non-L-dopa responsive Parkinsonism, autonomic dysfunction) within 5 years, especially if >50y/o**
- **Erectile dysfunction can precede ataxia by 5-10 years**
- **Notable cerebellar disability is seen within 2-3 years**
- **REM sleep disturbances, obstructive sleep apnea, and stridor are common**

Diagnostic Studies that May Help Differentiate MSA from SCA

- **The presence of dementia, ophthalmoplegia, or chorea suggest something other than MSA.**
- **MRI hyper- and hypo-intensities in the putamen**
- **18F-fluorodopa PET scanning may reveal basal ganglia abnormalities before the onset of clinical signs.**
- **Autonomic testing (heart rate variability, tilt table, sympathetic skin response, cardiac I-123-MIBG-SPECT) may show preclinical changes.**
- **Specific denervation may be seen on sphincter EMG.**

Idiopathic Cerebellar Ataxia

- **Type A--with dementia**
  (parenchymatous cerebellar cortical atrophy, prion diseases, Whipple's disease)

- **Type B--with tremor**

- **Type C--sporadic olivopontocerebellar atrophy**
  multiple system atrophy
  other Parkinson's plus syndromes (PSP)
  important to rule out SCA3

Treatable Causes of Non-Genetic Ataxia I

- **Congenital**
- **Infectious/Post-infectious--Ebstein-Barr**
  Enterovirus
- **HTLV1 /HIV/Syphillis**
  Lyme disease
- **Measles, Rubella, Varicella**
  Prion disease
  Whipple's disease
- **Post-anoxia, post-hyperthermia, post-trauma, and in chronic epilepsy**

Treatable Causes of Non-Genetic Ataxia II

- **Metabolic--acute thiamin (B1) deficiency**
  chronic vitamin B12 and E deficiencies
  autoimmune thyroiditis and low thyroid
- **Toxic------- <u>drug reactions</u>—amiodarone**
  cytosine arabinoside
- **5-fluorouracil**
- **phenytoin**
- **valproic acid**
- **<u>environmental</u>—acrylamide, alcohol,**
  organic solvents, organo-lead/mercury/tin,
- **inorganic bismuth/mercury/thallium**

Treatable Causes of Non-Genetic Ataxia III
Immune System Targeting the Cerebellum

- **Paraneoplastic---anti-Yo, Hu, Ri, MaTa, CV2**
  anti-Calcium channel
  anti-CRMP-5, ANNA-1,2,3, mGluR1
- **Other autoantibodies---**
  anti-gliadin (most common—reported also in the inherited syndromes as a possible secondary factor, treated with gluten-free diet and anti-immune therapy)
  anti-GluR2, GAD, MPP1, GQ1b ganglioside
- **Anti-immune therapy---steroids, plasmapheresis, IVIG, Rituxan, Cellcept, Methotrexate, and others.**

TREATMENT GOALS

- **Treat known causes--diet, replacement therapies**
  detoxification therapies
- **Improve performance--**
  symptom-specific drugs
  rehab/retraining of nerve pathways
- **Prevent innocent bystander effects--use it or lose it**
- **Improve activities of daily living and quality of life**
- **Slow up disease progression--the Robin Hood tactic**
  anti-oxidants
  neuroprotective drugs
  ?gene therapy, ?stem cell therapy

- The non-genetic ataxias are currently the most challenging area of research in cerebellar disease and the area most deserving of heightened effort in the search for susceptibility genes, environmental triggers, lifestyle factors, and age-related influences.
- They stand to benefit most from the National Ataxia Registry and Database.