Cerebellar Disorders

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Symptoms of cerebellar disorders

- Unsteadiness
- Dizziness
- Falls
- Slurred speech
Signs of cerebellar disease

- Gait and truncal ataxia
- Dysarthria
- Eye movement abnormalities
- Limb ataxia- tremor
- Dysdiadochokinesis
The two most important features?
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- Age at onset
- Course
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  - Early- Congenital, autosomal recessive,
  - Adult- ADCA, alcohol, paraneoplasia, vascular

- Course
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• Age at onset
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  – Adult- ADCA, alcohol, paraneoplasia, vascular

• Course
  – Acute- Vascular
  – Subacute- Paraneoplasia, infection
  – Chronic- ILOCA, ADCA, MSA
Associated signs

- Other neurological signs
  - Pyramidal
  - Neuropathic
  - Ocular

- Other systems
  - Telangiectasia
  - Hepatosplenomegaly (Niemann-Pick)
Investigations

- Imaging
- Neurophysiology
- Blood tests
  - Genetic tests
  - Antibodies
  - Others
Exceptions:

FXTAS
Joubert's
Leucodystrophies
Thin CC
Inherited Ataxias

• Early onset (<20yrs) - Autosomal Recessive

• Late onset (>25yrs) - Autosomal Dominant

• X linked - very rare
  – ADL, Pelizaeus Merzbacher
  – FXTAS
Prevalence
(limited data)

- FRDA- 1.7-3.7 per $10^5$ (very much lower in east asia)
- SCAs 3-4 per $10^5$
- Sporadic ataxia 7-8.5 per $10^5$ in Europe perhaps 18 per $10^5$ in Japan
Prevalence  
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• Overall ~heredotoataxias ~10 per $10^5$
State of Play

ARCAs

• >20 genes for Recessive ataxias

• Clinically:
  – FRDA
  – Others
Core clinical features

• Progressive gait and limb ataxia
• Early onset
• Autosomal recessive inheritance
Core clinical features

- Progressive gait and limb ataxia
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  - Absent reflexes and extensor plantars
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  - Skeletal abnormalities - Pes cavus
    - Scoliosis
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  – Skeletal abnormalities - Pes cavus
    - Scoliosis
  – Cardiomyopathy
Additional features

- Nystagmus
- Optic atrophy
- Diabetes
- Deafness
Friedreich's Ataxia: Autosomal Recessive Disease Caused by an Intrinsic GAA Triplet Repeat Expansion

Victoria Campuzano,* Laura Montermini,* Maria Dolores Molto,† Luigi Pianese, Mireille Cossée, Francesca Cavalcanti,‡ Eugenia Monros, François Rodius, Franck Duclos,§ Antonella Monticelli, Federico Zara, Joaquin Cañizares, Hana Koutnikova, Sanjay I. Bidichandani, Cinzia Gelleria, Alexis Brice, Paul Trouillas, Giuseppe De Michele, Alessandro Filla, Rosa De Frutos, Francisco Palau, Pragna I. Patel, Stefano Di Donato, Jean-Louis Mandel, Sergio Cozoza, Michel Koenig,¶ Massimo Pandolfo‖

Friedreich's ataxia (FRDA) is an autosomal recessive, degenerative disease that involves the central and peripheral nervous systems and the heart. A gene, X25, was identified in the critical region for the FRDA locus on chromosome 9q13. The gene encodes a 210-amino acid protein, frataxin, that has homologs in distant species such as Caenorhabditis elegans and yeast. A few FRDA patients were found to have point mutations in X25, but the majority were homozygous for an unstable GAA trinucleotide expansion in the first X25 intron.
Atypical Friedreich’s

- Retained reflexes
- Presentation with cardiomyopathy
- Later age of onset- up to 63 yrs old
- Chorea
- Pseudo-dominant families
Clinical impact

• ‘Homozygous expansion, confirms diagnosis in over 97%
• The remainder are heterozygous plus point mutations
• Useful for detecting carriers-reduces risk 100 fold
• What and where are the compound heterozygotes?
Spliceosomes

No intron lariat.
Spliceosome does not dock.
Intron is not excised.

5' cap
Exon 1
Intron 1
GAA repeats
or nucleotide mutation

AG GT
Exon 2
Intron 2

AG
Exon 3

Defective processing of mRNA

Translation into abnormal protein (frataxin)
Management

- ECG
- Blood sugar
- Orthopaedic management
- Physiotherapy
Treatment

- No large scale double-blind controlled studies
- Some evidence
  - Vitamin E
  - Co-Enzyme Q10
  - Idebenone
  - N-Acetyl Cysteine
Autosomal recessive ataxias

Early-onset cerebellar ataxia with:
- Oculomotor apraxia – aprataxin, senataxin, ATM
- Hypogonadism
- Myoclonus (progressive myoclonic ataxia, Ramsay Hunt syndrome)
- Childhood/Congenital deafness
- Optic atrophy with or without mental retardation (including Behr’s syndrome)
- Cataract and mental retardation (Marinesco-Sjögren's syndrome)
- Pigmentary retinopathy

Late-onset
Western blot of different proteins

- ATM
- ATM overexposed
- Senataxin
- hRad50
- Nbs1
- hMre11
- TDP1
- Aprataxin

Samples:
- Normal
- A-T
- AOA2
- Danish patient

Patients:
- S.
- G.
- B.
- A.
- R.
- C.
- H.
Neurological features of vitamin E deficiency

- Abetalipoproteinemia
- Cholestatic Liver Disease
- Cystic Fibrosis
- Intestinal Resection
- Isolated Deficiency (AVED)
AVED

- Titubation
- Hyporeflexia
- Tremor helped by alcohol
- Treatment stops progression
  - Improvement variable
State of Play

ADCAs

• 26 SCAs currently assigned
  – Note SCA number currently in the 30s!

• Of the 26 genes identified in 16
  – Note merging of some ‘loci’ eg 15/16 & 19/22
ADCA - Clinical Classification

• ADCA I - “ataxia plus”
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<th>Date</th>
<th>Event</th>
<th>Description</th>
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<td>Feb 13th 95</td>
<td>Admitted</td>
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<tr>
<td>July 6th 95</td>
<td>Discharged</td>
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**Physician**

Dr. Lowery

**Name**

William Brown

**Married**

Age 25

**Address**

13 High St. Earl's Court

**Occupation**

Clerk

**Disease**

Pulmonary Tuberculosis

**History**

Cough for 1 year

**Examination**

Lungs: Excessive breath sounds right upper lobe

**Treatment**

[Handwritten note]
ADCA - Clinical Classification

- ADCA I - “ataxia plus”
  - Extrapyramidal
  - Supranuclear ophthalmoplegia
  - Neuropathy
  - Dementia
  - Psychiatric disorder
ADCA - Clinical Classification

- ADCA I - “ataxia plus”
- ADCA II - ?
ADCA - Clinical Classification

- ADCA I - “ataxia plus”
- ADCA II - pigmentary macular dystrophy
- ADCA III - “pure” cerebellar ataxia
<table>
<thead>
<tr>
<th>ADCA Type</th>
<th>Genetic tests (widely available)</th>
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<tr>
<td>ADCA I</td>
<td>SCA 1, 2, 3,</td>
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<td>ADCA II</td>
<td>SCA 7</td>
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<tr>
<td>ADCA III</td>
<td>SCA 6</td>
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Clinico-genetic correlates

• SCA 3 - Extrapyramidal features
• SCA 2 - Reflexes
  Slow saccades
• SCA 12 - perhaps more common in India
• SCA 14 - Dystonia
• SCA 17 - HD look-a-like (also consider DRPLA)
Trinucleotide Repeats

CAG
- HD
- DRPLA
- SCA 1,2,3,6,7 and 17
- SBMA

Others
- Fragile X
- Myotonic dystrophy
- Fra 16
- Friedreich’s ataxia
- ?SCA 8
Similarities

- All have modest expansion of CAG
- In coding region
- Neurodegenerative
- Paternal transmission effects
- Variable prevalence
  - at least in part determined by ‘pre-mutation’ status of normal allele
SCA 6

- CACN1A- 3 allelic forms
  - FHM
  - EA2
  - SCA6
1. **Patients**
   - Sample collection
   - Genetic linkage analysis
   - Positional cloning
   - Gene characterization

2. **Disease gene**
   - Assays for screening
   - Cell culture & animal models
   - Gene characterization
   - Therapeutics development

3. **Phenotype characterization**
   - Cell culture & animal models
   - Gene characterization
ILOCA

- An heterogeneous group
- Often unknown
- MSA-C
MSA-History

- Dejerine and Thomas 1900
- SND recognised 1960
- Shy-Drager report 1960
- Graham and Oppenheimer coin MSA 1969
- GCIs -1989
- Role of $\alpha$-synuclein 1998
- Consensus criteria 2008
MSA – a clinical diagnosis with Glial cytoplasmic inclusions
• Carriers of ‘premutation’ FMR alleles (55-200) may present with ataxic syndrome in mid late life.

• Males>>>females

• Neurodegenerative
Cerebellar ataxia - long differential

- Sorted mostly by age of onset and course
- Additional features also help differentiate
  - Signs
  - Investigations
Themes

- Dynamic repeats- especially CAG
- DNA repair
- Mitochondrial dysfunction
- Episodes and ion channels
- Miscellaneous mechanisms
  - Eg Refsums, ADL, Gangliosidosis, ARSACS, PHARC
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