Sporadic ataxia and multiple system atrophy

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Ataxia

- Definition: Incoordination (clumsiness) of movement not due to weakness
- Literal meaning: “absence of order”
- Results from disease of
  - Cerebellum
  - Vestibular system
  - Peripheral nerves
Ataxia

• Affects speech, eye movements, limb movements, trunk stability, can result in falls
• This discussion limited to cerebellar ataxias

Causes of sporadic ataxia

• Acquired ataxias
  – Trauma
  – Vascular disease
  – Infections
Causes of sporadic ataxia

• Acquired ataxias (continued)
  – Toxins
  – Neoplasms
  – Paraneoplastic disease
  – Other immune disorders
  – Metabolic diseases
  – Fragile X tremor/ataxia syndrome
  – Conversion reaction

• Sporadic degenerative ataxias: SCD, MSA
Outcome of sporadic degenerative ataxias

- Gilman et al Neurology 2000;55:527
  - Observed 51 patients with sporadic adult onset cerebellar ataxia over 14 years
  - All fully evaluated for identifiable causes
  - 17 evolved to MSA
  - 34 showed worsening ataxia
  - Survival analysis: 24% of sporadic adult onset ataxia patients will evolve into MSA within 5 years
Abele et al. Brain 2002;125:961
- Evaluated 112 patients with sporadic ataxia
  - Onset over age 20 years
  - Median age 56 years
  - No identifiable family history
- In 13% a genetically mediated ataxia (SCA 2, 3, 6 and Friedreich’s ataxia)
Outcome (continued)

• Abele et al Brain 2002;125:961
  – In 29% patients met criteria for possible or probable multiple system atrophy
  – In 58% diagnosis remained undetermined
  – Conclusion: About 50% of sporadic adult onset cerebellar ataxia patients cannot be diagnosed initially
Multiple System Atrophy

• An adult onset, sporadic, progressive neurodegenerative disease
• Characterized clinically by varying severity of
  – Parkinsonian features
  – Cerebellar ataxia
  – Autonomic failure
  – Urogenital dysfunction
  – Corticospinal disorders
Multiple System Atrophy

• Presenting symptom varies
  – Parkinsonian features in a majority
  – Cerebellar features less frequently
  – Autonomic failure or urogenital dysfunction can precede other symptoms by months to years

• Described by major feature at any single time
  – MSA-P: Predominantly parkinsonian features
  – MSA-C: Predominantly cerebellar ataxia
Neuropathological features of MSA

• Glial and neuronal inclusions
  – Glial cytoplasmic inclusions (GCIs)
    – The predominant pathology
  – Neuronal cytoplasmic inclusions (NCIs)
  – Glial nuclear inclusions (GNIs)
  – Neuronal nuclear inclusions (NNIs)

• Inclusions contain alpha-synuclein
Cytoplasmic inclusions in MSA

Wakabayashi and Takahashi 2006

Glial Cytoplasmic Inclusions

Neuronal Cytoplasmic Inclusions

Neuronal Nuclear Inclusions
Protein abnormality links PD and MSA

- GCIs contain misfolded alpha-synuclein
- Alpha-synuclein normally a neurotransmitter chaperone
- Alpha-synuclein a major component of Lewy bodies and Lewy filaments, the defining characteristic of Parkinson’s disease, dementia with Lewy bodies
Other neuropathological features

- Neurodegeneration in high concentration areas of glial and neuronal inclusions
  - Motor and supplementary motor cortex
  - Internal and external capsules
  - Basal ganglia
  - Brainstem (pons, s. nigra, inferior olives, autonomic ganglia)
  - Cerebellum
  - Spinal cord (intermediolateral cell column, Onuf’s nucleus)
Disease onset and evolution

- Parkinsonism: slowness of movement, rigidity, masked face, sudden falls, trouble turning in bed, difficulty getting out of a chair, soft speech
- Idiopathic sporadic cerebellar degeneration: ataxia of speech, gait, limb movements, deterioration of handwriting, falls
- Autonomic insufficiency: light headedness on standing (orthostatic hypotension), urinary urgency, frequency, incomplete bladder emptying, inability to sweat, constipation
• **Definite MSA:** Requires postmortem validation
  – Neuropathologic findings of widespread and abundant CNS α-synuclein-positive GCIs in association with neurodegenerative changes in striatonigral or olivopontocerebellar structures
• Probable MSA
  – A sporadic, progressive, adult (>30 years) onset disease characterized by:
    • Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or
    • An orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and
Probable MSA (continued)

*and*

- Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability)

*or*

- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)
Consensus Criteria
Neurology 2008:71;670-676

• Possible MSA
  – A sporadic, progressive, adult (>30 years) onset disease characterized by:
    • Parkinsonism (bradykinesia with rigidity, tremor or postural instability) or
    • A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

and
• Possible MSA (continued)

  and

• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA)

  and

• At least one of the additional features shown in the following tables
Consensus Criteria
Additional features of possible MSA

• For MSA-C or MSA-P:
  – Babinski sign with hyperreflexia
  – Stridor

• For possible MSA-P:
  – Rapidly progressive parkinsonism
  – Poor response to levodopa
  – Postural instability within 3 years of motor onset
  – Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
  – Dysphagia within 5 years of motor onset
Consensus Criteria
Additional features of possible MSA

• For possible MSA-P (continued)
  – Atrophy on MRI of putamen, middle cerebellar peduncle, pons or cerebellum
  – Hypometabolism on FDG-PET in putamen, brainstem or cerebellum

• For possible MSA-C:
  – Parkinsonism (bradykinesia and rigidity)
  – Atrophy on MRI of putamen, mcp, or pons
  – Hypometabolism on FDG-PET in putamen
  – Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET
Long-term outcome

• Initial symptoms usually in 6th decade
• Incidence rate 0.6 cases/100,000 people
  • Above age 50, incidence rate 3/100,000
• Median life span 9 years from symptom onset (Watanabe et al 2002)
  • Highly variable survival, individual cases up to 15 years
• Survival at 5 years 84%, at 10 years 40%
Two clinical trials in progress

• Rasagiline, an inhibitor of monoamine oxidase type B (MAO-B), approved for treatment of Parkinson’s disease
  – Rationale for use in PD: Slows biochemical destruction of dopamine
  – A delayed-start trial provided evidence of slowed rate of neurodegenerative changes in PD
  – Clinical trials fully enrolled in US and Europe in MSA-P
  – Sponsored by Teva Pharmaceuticals
Clinical trials in progress

• Rifampicin
  • Antibiotic useful for treatment of mycobacterium species (tuberculosis, leprosy)
    – Mouse model of MSA
      – Accumulation of misfolded alpha-synuclein
      – Clinical findings replicating aspects of human MSA.
    – Rifampicin removed accumulated alpha-synuclein and prevented new deposits
    – A clinical trial will begin in March 2011
    – Sponsored by NIH (Phillip Low, David Robertson, Sid Gilman, PIs)
Summary and conclusions

• Sporadic ataxias
  – Caused by multiple types of diseases
  – Clinical evaluation must seek these diseases and for hereditary ataxia
  – At least 50% of sporadic degenerative ataxias progress slowly with preservation of function
  – About 25% of sporadic degenerative ataxia patients progress to MSA
  – Two clinical trials of MSA are beginning with hope of disease-modification with slowing of progression
The End