Neuropathology of multiple system atrophy: an update

Alpha-synuclein: the gateway to parkinsonism
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Professor Janice Holton
Director of Neuropathology
Queen Square Brain Bank
UCL Institute of Neurology
London, UK

Overview

• Review the major pathological features of MSA
  – Macroscopic appearances
  – Histology
• Clinico-pathological correlations in MSA
• Discuss glial cytoplasmic inclusions in MSA
  – Contribution to pathogenesis
  – Summarise aspects of GCI formation
  – Can α-synuclein mutations tell us anything about MSA?

Macroscopic features

• Atrophy and dark discoloration of the putamen
• Cerebellar cortical atrophy
• Atrophy and discoloration of the cerebellar hemispheric white matter with preservation of the superior cerebellar peduncle
• Pallor of the substantia nigra
• Atrophy of the pontine base
• Atrophy of the inferior olivary nucleus
Neuropathological subtypes of MSA

1. Olivopontocerebellar atrophy (OPCA)
   - Atrophy of inferior olive
   - Atrophy of pontine base
   - Loss of transverse fibres
   - Preserved pontine tegmentum and superior cerebellar peduncle
   - Cerebellar cortical atrophy
   - Discoloured and reduced cerebellar white matter

2. Striatonigral degeneration (SND)
   - Atrophy and discolouration of putamen
   - Lack of substantia nigra

3. Mixed SND/OPCA

4. Minimal Change MSA
   - Neuronal loss restricted to nigra, locus coeruleus
   - Widespread GCIs

Cellular inclusions and diagnosis of MSA

Gliial cytoplasmic inclusion
Gliial nuclear inclusion
Neuronal cytoplasmic inclusion
Neuronal nuclear inclusion
Neurofil thread

Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy

J. G. Trojanowski and T. Revesz for the Neuropathology Working Group on MSA

Widespread GCIs with neurodegeneration are the criteria for definite neuropathological diagnosis of MSA.
**Clinicopathological correlations in MSA**

**Long duration →15 years (n = 4)**

<table>
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<th>Long disease duration MSA vs control MSA</th>
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<td>LD-MSA vs Control MSA</td>
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<td>GCI</td>
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<td>Control: LD-MSA vs control MSA, p&lt;0.002</td>
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<td>NCI</td>
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<td>Control: LD-MSA vs control MSA, p&lt;0.001</td>
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<td>Neuronal loss</td>
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<td>No significant differences</td>
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<tr>
<td>Gliosis</td>
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<td>• Long duration MSA may represent a more benign disease variant</td>
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- Delayed onset of autonomic dysfunction associated with favorable clinical outcome
- Widespread pathology in cortical, striatogiral, olivopontocerebellar regions

**Minimal change MSA**

- Neuronal loss restricted to nigra and locus coeruleus, n=8 (selected from 135 cases)
- Controls: 8 with classical disease course and progression
- Caudate and nigra: Greater NCI burden in MC-MSA
- GCI no difference from control MSA
- 3 with interrupted disease, 3 with sudden death (SUO)
- SUD:
  - Shorter disease duration 5.3±1.3y vs. 8±3.3 y, p=0.2
  - Younger onset: 38±4.0y vs. 57±11.5y, p=0.02
  - Aggressive disease course (most milestones reached in 3 yrs)
- Minimal change MSA may represent a more aggressive disease variant

**MSA cognitive impaired vs age matched MSA, normal cognition (n=9)**

- No difference in: GCI burden, NCI burden, neuronal loss, Aβ load, Braak tau staging (not >4), CAA, small vessel disease
- Neuropathological substrate of cognitive impairment in MSA remains to be elucidated
The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations

Frequency of GCPs correlates with neuronal loss and disease duration implicating GCPs in neurodegeneration

Determining the mechanism of GCI formation is critical to understanding neurodegeneration in MSA

Understanding the mechanism of GCI formation

- In MSA α-synuclein relocates from myelin to oligodendroglial cell body
- LRRK2 is present in oligodendroglial cell body
- Cell body becomes enlarged
- Myelin degradation occurs
- Subsequent deposition of fibrillar α-synuclein forming GCI


Understanding the mechanism of GCI formation

Initiating factors?
Neuroinflammation?

Altered structure?
Influence on protein degradation?
Influence on cell-cell transmission?

Source?
Synthesised by oligodendroglia?
From neurons?

Genetic influences in MSA
Recombinant monomeric and oligomeric a-synuclein taken up by oligodendrocytes.

In rat model expressing human a-synuclein in nigral neurons and axons: demonstrated transfer of a-synuclein from neurons into grafted OPC and mature oligodendrocytes.

**Table:**

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**Legend:**
- PD: Parkinson's disease
- PD-like: Parkinson-like disease
- DLB: Dementia with Lewy bodies
- AD: Alzheimer's disease
- MCI: Mild cognitive impairment
- Controls: Healthy controls

**Figure:**

Overproduction or mutation of a-syn may predispose to GCI formation.

Mutation: structural alteration, altered fibril formation kinetics or impaired degradation?
Conclusions

- Clinicopathological studies
  - Long disease duration and late autonomic failure - benign disease sub-type?
  - Minimal change MSA - milder phenotype, younger onset?
  - Cognitive impairment in MSA is not related to α-synuclein load and distribution or to other concomitant pathologies
- α-synuclein containing GCIs are important in MSA pathogenesis
- There are changes in oligodendrocytes before the aggregation of α-synuclein – understanding triggers could be important
- Oligodendrocytes may:
  - Synthesise α-synuclein
  - Take up α-synuclein from neurons
- Altered biochemical properties of α-synuclein may be important in GCI formation – SNCA mutations may be informative