Right under our noses: olfactory pathology in central nervous system demyelinating diseases

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*Presenter has no disclosures

Olfactory Pathology in Demyelinating Diseases

Background

- Olfactory dysfunction is a common feature in multiple sclerosis (MS)
  - 20-50% of patients exhibit olfactory deficits on testing
    (Pinching et al., 1977; Hawkes et al., 1997; Doty et al., 1997; Lutterotti et al., 2011; Rolet et al., 2013)

- Olfactory anatomy:
  1. Olfactory neuroepithelium
  2. Olfactory bulb and tract
  3. Olfactory brain

- What is the anatomic substrate for loss of smell in MS?
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Background

- At end of 19th century → Gowers described MS pathology in detail

Gowers, A Manual of Diseases of the Nervous System, 1886

- Zimmerman and Netsky (1950) → No olfactory bulb/tract DM in MS (n=8)

Olfactory loss

$\alpha$

MRI lesion burden in olfactory brain

Doy et al., NEJM 1997

- Shifted search for olfactory dysfunction in olfactory brain
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Research Hypothesis

That olfactory bulb/tract are pathologically affected in MS and in other demyelinating diseases

Case Selection

- Human autopsy cohort of pathologically confirmed cases

**Demyelinating** Diseases
- Multiple sclerosis (MS) (n=17)
- Neuromyelitis optica (NMO) (n=3)
- Acute disseminated encephalomyelitis (ADEM) (n=7)

**Neuroinflammatory Disease**
- Herpes Simplex Encephalitis (HSE) (n=3)

**Neurodegenerative Disease**
- Alzheimer's Disease (AD) (n=4)

**Non-neurologic Controls**
- (n=8)
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Materials and Methods

• Coronally sliced brains realigned → olfactory bulbs/tracts sampled

• Subjacent inferofrontal cortex and hippocampus sampled, where available

Demyelination

• Areas of DM quantified and related to total sampled area
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Materials and Methods

Inflammation

- T- and B-lymphocytes and macrophages/microglia scored semi-quantitatively

0 no cells/field; + 1 cell/field; ++ 2-4 cells/field; +++ > 4 cells/field

Axonal loss

![Palmgren Silver stain for axons](image)

Results

Cohort

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Control</th>
<th>M5</th>
<th>NMO</th>
<th>ADEM</th>
<th>HSE</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>65.0 (52-77)</td>
<td>55.2 (15-76)</td>
<td>56.5 (18-64)</td>
<td>54.4 (10-59)</td>
<td>56.0 (18-47)</td>
<td>76.3 (75-80)</td>
</tr>
<tr>
<td>Duration of Disease</td>
<td>N/A</td>
<td>8.2 yrs (4-32 yrs)</td>
<td>8.0 yrs (1-15 yrs)</td>
<td>7.1 days (3-14 days)</td>
<td>3.0 days</td>
<td>10.8 yrs (8-15 yrs)</td>
</tr>
</tbody>
</table>

- Age and duration of disease differed significantly b/w disease groups
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Results

Demyelination

- Myelination pattern in olfactory bulb/tract was complex

0/8 cases (0%)

• MS / NMO plaques → all chronic; ADEM plaques → all active

• HSE, AD, and non-neurologic controls → no demyelination
Results

Inflammation

- Olfactory bulb/tract inflammation observed in all disease groups (in parenchyma, perivascular space, meninges)

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**Results**

**Inflammation**

![Graph showing inflammation levels](image)

**Macrophages (PG-M1)**

**T-cells (CD3+)**

- Striking inflammation in acute neurologic diseases
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Results

**Axonal Loss**

![Graph showing semiquantitative score for Axonal Loss across different conditions: Control, MS, NMO, ADEM, HSE, AD.](image)

- Axonal loss was most pronounced in MS and Alzheimer’s disease.

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**Olfactory Pathology in Demyelinating Diseases**

**Results**

**Relationship between olfactory and cortical demyelination**

**Inferofrontal Cortical Lesions**

- 180 lesions from 73 inferofrontal cortical blocks juxtaposed to analysed olfactory bulb/tract from 22 cases (MS, n=15; ADEM, n=7)

**Hippocampal Lesions**

- 23 lesions from 27 hippocampal blocks from 12 cases (MS, n=7; ADEM, n=5)

![Graph showing proportional DM for Inferofrontal Cortex and Hippocampus.](image)

**p = 0.01**
Conclusions

• Olfactory bulb/tract demyelination:
  - frequent
  - can occur early
  - can be highly inflammatory
  - relates to subjacent cortical DM

• Alternative explanation for loss of smell in MS and other demyelinating diseases?

• Role of olfactory system in pathogenesis of demyelinating diseases?

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