Neurology's Video Journal Club
Multiple Sclerosis / Autoimmune Neurology Series

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Differences in Age-related Retinal and Cortical Atrophy Rates in Multiple Sclerosis

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Introduction

**Neuro-axonal loss in multiple sclerosis (MS):**

- Relevant *substrate* of *disability progression*
- Occurs *from the earliest phases* of the disease, being *more severe in progressive MS patients*
- **Pathophysiology**
  - Direct result of *immune-mediated*, myelin-targeted inflammatory events
  - Longer-term consequence of *chronic inflammation, remyelination failure, aberrant glial cell activation, mitochondrial dysfunction and oxidative stress*
  - Aging and immunosenescence

*Magnetic resonance imaging (MRI) and optical coherence tomography (OCT) are accurate tools to quantify atrophy of the brain and of the retina*

**What is missing**

- How do *different age-associated mechanisms* affect the *rate of neurodegeneration* in different CNS structures?
Research hypothesis

Research question

• To explore the differences in age-related retinal and cortical atrophy rates in MS

The brain cortex and retina have different cytoarchitectures

• Retina: greater proportion of tissue volume coming from neurons/axons
• Cortex: greater heterogeneity of neuronal subtypes and presence of oligodendrocytes

Research hypothesis

• Due to different impacts of inflammation across the disease course, neurodegeneration is faster in the first stages of MS
• By evaluating the retina (ganglion cell-inner plexiform layer [GCIPL] macular volume), OCT can help in measuring inflammation-mediated neuronal cell body loss, earlier than MRI metrics for assessing of neurodegeneration

Relevance

• Understanding these different dynamics can affect therapeutic decision-making and help with the design of clinical trials that will use measures of neurodegeneration as their outcomes
## Methods

### Study populations

University of California, San Francisco (UCSF EPIC study)

<table>
<thead>
<tr>
<th></th>
<th>OCT MS cohort (n=597)</th>
<th>MRI MS cohort (n=432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) [years]</td>
<td>45.3 (11.0)</td>
<td>41.8 (9.6)</td>
</tr>
<tr>
<td>Sex (female/male) [%]</td>
<td>69% / 31%</td>
<td>69% / 31%</td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td>90% RRMS, 10% PMS</td>
<td>14% CIS, 86% RRMS</td>
</tr>
<tr>
<td>Mean disease duration (SD) [years]</td>
<td>11.6 (9.7)</td>
<td>8.0 (8.3)</td>
</tr>
<tr>
<td>Median EDSS score (IQR)</td>
<td>2.0 (1.5;3.0)</td>
<td>1.5 (1.0;2.0)</td>
</tr>
<tr>
<td>Mean Longitudinal imaging (SD) [years]</td>
<td>4.5 (2.4)</td>
<td>10.0 (3.4)</td>
</tr>
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</table>

### Cortical gray matter (CGM) volume

**Spectral domain OCT**
(Spectralis; Heidelberg Engineering, Heidelberg, Germany)
**Quality:** OSCAR-IB criteria
**Reporting data:** APOSTEL guideline
**OCT measure:** macular GCIPL thickness

### MRI acquisition and analysis

**T1-weighted images:**
MRI outcome: **Cortical gray matter (CGM) volume**
[Freesurfer]
Results

**GCIPL macular volume**

<table>
<thead>
<tr>
<th>Age at the time of first OCT younger than 35 y</th>
<th>Age at the time of first OCT older than 35 and younger than 41 y</th>
<th>Age at the time of first OCT older than 41 and younger than 49 y</th>
<th>Age at the time of first OCT older than 49 y</th>
</tr>
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<tbody>
<tr>
<td>GCIPL decrease, µm/y (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 (0.41–0.59)</td>
<td>0.22 (0.14–0.31)</td>
<td>0.26 (0.19–0.33)</td>
<td>0.27 (0.20–0.33)</td>
</tr>
<tr>
<td>GCIPL % decrease per year (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7 (0.38–0.85)</td>
<td>0.29 (0.18–0.43)</td>
<td>0.34 (0.23–0.43)</td>
<td>0.37 (0.27–0.43)</td>
</tr>
</tbody>
</table>

**CGM volume**

<table>
<thead>
<tr>
<th>Age at the time of first MRI younger than 35 y</th>
<th>Age at the time of first MRI older than 35 and younger than 41 y</th>
<th>Age at the time of first MRI older than 41 and younger than 49 y</th>
<th>Age at the time of first MRI older than 49 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGM volume decrease, cm³/y (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.2 (7.9–8.8)</td>
<td>7 (6.5–7.4)</td>
<td>6 (5.4–6.3)</td>
<td>5.4 (4.9–5.8)</td>
</tr>
<tr>
<td>CGM volume % decrease per year (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3 (1.25–1.4)</td>
<td>1.1 (1.04–1.18)</td>
<td>0.97 (0.89–1.03)</td>
<td>0.9 (0.82–0.97)</td>
</tr>
</tbody>
</table>
The differences between age quartiles in the rates of GCIPL and CGM atrophy remained unchanged after accounting for the number of previous clinical relapses.
Sensitivity analysis / Effect of disease duration

- **GCIPL macular volume**
  - A. GCIPL by disease duration (years)
  - Difference between the youngest age category and the other age categories was maintained with disease duration shorter than 10 years.
The rates of atrophy maintained similar slopes within the various age categories for MS patients on no treatment and for MS patients treated with modest-efficacy treatments (interferons, glatiramer acetate, teriflunomide).

Different pattern of neurodegeneration across ages in MS patients treated with moderate-efficacy (fingolimod, dimethyl fumarate) and high-efficacy treatments (natalizumab, anti-CD20 monoclonal antibodies, alemtuzumab).
Discussion

• A faster rate of atrophy of the GCIPL and CGM was observed in the youngest patients with MS that slowed with age.

• Possible pathophysiological mechanisms:
  - Progressive reduction of acute pro-inflammatory status and inflammatory events with aging.
  - Astrogliosis, higher diffuse amount of activated microglia, and capacity for neuronal self-protection may counterbalance atrophy.

• Age is a critical consideration in the design of clinical trials using OCT and MRI as outcome measures.
Discussion

- **Changes** in the rate of neurodegeneration are **different** in the retina and brain cortex
  - Above the first age quartile, the rate of atrophy in the GCIPL remains relatively constant
  - The rate of CGM atrophy progressively declines with age, but never seems to fully stabilize

- Possible **pathophysiological** and **methodological explanations**:
  - Different **tissue susceptibility** to inflammation-related damage due to different tissue cytoarchitecture, protein distributions and immunologic targets, as well as variable neuronal vulnerability to MS-related damage
  - Differences in the **sensitivity**, **specificity** and **reproducibility** of OCT and MRI in detecting tissue atrophy

- The different patterns of changes in GCIPL and CGM in MS patients on **moderate-efficacy** and **high-efficacy DMTs**, suggesting that these therapies may potentially **alter the trajectory of neurodegeneration** in MS, especially in young patients
Strengths of the study

- **Large sample size**, with **standardized** and **systematic data** collection with a **longitudinal assessment** for several years
- Relevant **sensitivity analyses** (effects of DMTs, disease duration, clinical relapses)
- Eyes with a history of optic neuritis were not excluded to evaluate a representative cohort of MS patients and to better explore the **associations** between **inflammatory activity** and **neurodegeneration**
Limitations

• The age of the first OCT was older than the age of the first MRI
  - Many MS patients started undergoing MRIs several years before starting to have annual OCTs

• The linear mixed-effects model does not allow to take into account nonlinear effects of neurodegeneration in MS

• Using DMTs as time-varying covariates did not account for the potential carryover effect and delayed onset of action of medications
Future steps

• Evaluation of longitudinal changes of **CGM volume at regional level**
• Evaluation of **additional CNS regions**
  - Thalamus and deep GM nuclei
  - Hippocampus
  - Cerebellum
  - Spinal cord
• Impact of **clinical relapses** according to **functional system involved**
• Impact of **focal WM lesions** according to **CNS topography**
• Impact of **specific DMTs**
Conclusions

Early use of high-efficacy DMTs
Best window of therapeutic opportunity