

# The Role of Retinal Hyper-Reflecting Foci in Axonal Damage and Retinal Vascular Density in Multiple Sclerosis



**Sin**  
SOCIETÀ ITALIANA DI NEUROLOGIA

## Authors

Alessia Castiello<sup>1</sup>, Antonio Carotenuto<sup>2</sup>, Gilda Cennamo<sup>1</sup>, Michele Rinaldi<sup>1</sup>, Antonio Esposito<sup>1</sup>, Giuseppe Corsini<sup>1</sup>, Valerio Nicoletta<sup>1</sup>, Davide Ranucci<sup>1</sup>, Maria Petracca<sup>3</sup>, Marcello Moccia<sup>4,5</sup>, Roberta Lanzillo<sup>1</sup>, Vincenzo Brescia Morra<sup>1</sup>, Ciro Costagliola<sup>1</sup>.

## Introduction

Optical Coherence Tomography (OCT) is a key tool for assessing disease activity in Multiple Sclerosis (MS), particularly in detecting neuro-axonal atrophy, which correlates with brain atrophy. Beyond atrophy, vascular damage and microglial activation are pivotal in MS pathology. OCT Angiography (OCTA) further enables the evaluation of retinal vascular density (VD), which is reduced in MS patients in the foveal region and optic nerve head (ONH). Increasing evidence suggests that retinal hyper-reflecting foci (HRF) might be markers of activated and proliferating microglia, though their role is debated due to potential associations with microvascular anomalies. This study investigates the relationship between HRF, axonal damage, and Vessel Density in relapsing-remitting MS (RRMS).

## Methods

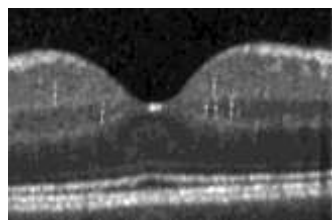
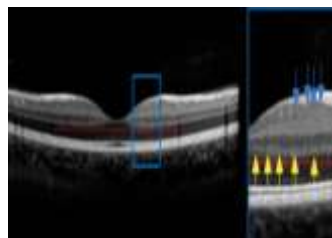
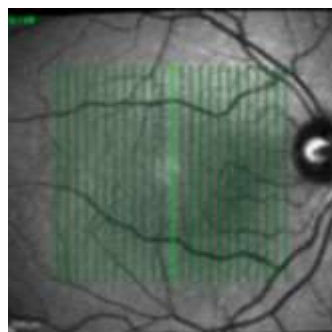
We evaluated ganglion cell complex (GCC), retinal nerve fiber layer (RNFL) and vessel density (VD) in superficial capillary plexus, deep capillary plexus, the optic nerve head (ONH) whole image, within the ONH (inside disc VD), and radial peripapillary capillary plexus in relapsing-remitting MS patients through Optical Coherence Tomography Angiography (OCT-A). Patients with history of optic neuritis were excluded. HRF were defined as isolated, small-size (<30  $\mu\text{m}$ ), punctiform elements with moderate reflectivity without any back shadowing in the area included between two lines traced at 1,500  $\mu\text{m}$  from the center of the fovea. Association between OCT-Spectral Domain, OCT-A and HRF was assessed through Correlations between SDOCT and OCTA parameters were assessed using linear mixed model using age and sex as covariates and subject as random factor.

## Results

We enrolled 19 RRMS patients (7 females; mean age  $38.9 \pm 14.6$  years; median disease duration of 5 (3 – 10) years and a median EDSS of 2.5 (1.5 – 5)) for a total of 38 eyes. Median number of HRF per subject was 4 (1 – 7). We found a positive inter-eye correlation for Hyper Reflecting Foci (coeff. 0.50,  $p=0.03$ ). Number of HRF resulted associated with Retinal Nerve Fiber Layer (correl. coeff. = -35.3,  $p=0.03$ ) and with inside disc Vessel Density (correl. coeff. = -2.00,  $p=0.01$ ).

## Conclusions

HRF correlate primarily with axonal damage, such as reduced retinal nerve fiber layer thickness, rather than with vascular parameters. This suggests that HRF are epiphenomena of activated microglia driving chronic inflammation, which ultimately leads to axonal loss and reduced vascular supply demand in highly neuronal regions like the Optic Nerve Head. These findings position HRF as potential biomarkers of microglial activation and neurodegeneration in MS, further researches into their role in disease monitoring and therapy are needed.



## References

- Puthenparampil et al., *Hyper-Reflecting Foci in Multiple Sclerosis Retina Associate With Macrophage/Microglia-Derived Cytokines in Cerebrospinal Fluid.* *Front Immunol.* 2022 May 19;13:852183.
- Klyszcz P et al, *Hyperreflective retinal foci are associated with retinal degeneration after optic neuritis in neuromyelitis optica spectrum disorders and multiple sclerosis.* *Eur J Neurol.* 2025 Jan;32(1):e70038



**55° CONGRESSO  
SOCIETÀ ITALIANA  
DI NEUROLOGIA**