OCT and OCT angiography in differential diagnosis of MS: the retina as a window on the CNS

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Introduction

MS is an inflammatory and demyelinating CNS disease that is often misdiagnosed due to overlapping clinical and radiological features with other MS-like disorders and misdiagnosis can lead to overdiagnosis and overtreatment. Diagnostic criteria, designed to reduce the time to diagnosis and initiation of treatment, prioritize high sensitivity instead of specificity. As a result, they may encompass syndromes that exhibit clinical or radiological red flags suggestive of alternative diagnoses, despite formally meeting the criteria for MS. In this context, the identification of biomarkers specific to MS is of paramount importance. The perivenular location (PVL) of brain white matter lesions—visualized as the central vein sign (CVS) on T2*-weighted MRI—has emerged as a highly specific imaging marker for MS. Syndromes with an MS-like clinical course but a low frequency of PVL may represent distinct pathological entities, potentially associated with primary arteriolar involvement. This hypothesis can be explored through non-invasive imaging modalities targeting the retina, optic nerve, and the retinal vascular network. Optical coherence tomography (OCT) and OCT angiography (OCTA) are non-invasive techniques employed to assess the structural integrity of the retina and optic nerve, as well as to evaluate the microvascular architecture of the retinal vasculature.

Aims and methods

The aim of this study is to investigate the contribution of OCT and OCTA in the differential diagnosis of MS-like syndromes. It seeks to evaluate structural and vascular retinal differences among patients with typical MS, MS with clinical or radiological red flags suggestive of alternative diagnoses (MS-plus), and non-MS (nMS) as CNS diseases characterized by distinct pathogenetic mechanisms. Patient enrolled underwent to OCT and OCTA and the following parameters were measured in each eye separately: optic disk nerve head whole, RCPC and lamina cribrosa vessel density, vessel density of superficial capillary plexus (SCP) and deep capillary plexus (DCP), as well as area, perimeter, and circularity of the foveal avascular zone FAZ. A subgroup of patients performed 3T MRI with SWI sequences and CVS analysis.

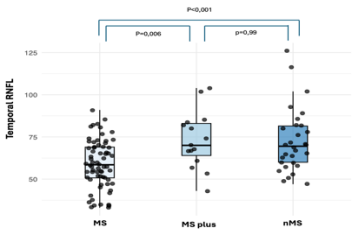
Results

The whole population enrolled is composed by 57 pts who underwent to a diagnostic workup for MS differential diagnosis. 3 subgroups were identified: 34 pts were MS according to 2017 McDonald Diagnostic Criteria, 8 pts were MS according to 2017 McDonald Diagnostic Criteria and with at least clinical or radiological red flag (MSplus), and 15 pts were not MS (nMS). Basal characteristics are showed in **Table 1**. The nMS group is composed by MOGAD (n=2), NMOSD (n=1), Susac Syndrome (n=2), Primary CNS Lymphoma (n=1), vascular leukoencephalopathy (n=4), leukoencephalopathy in Psoriasic Arthritis (n=2), leukoencephalopathy in Sjogren Syndrome (n=1), leukoencephalopathy in APS (n=1), and myelitis (n=1). A subgroup of 19 pts (MS n=10 MSplus n=3 nMS n=6) performed CVS analysis (CVS+ if PVL>50% of all white matter lesions).

Table 1. Basal characteristics of whole population and subgroups

	Whole population (57 pts)	MS (34 pts)	MS plus (8 pts)	nMS (15 pts)
Sex	44 (77,2%) F	24 (70,6%) F	8 (100%) F	12 (80%) F
Mean age at disease onset (years, SD)	38,4 (11,4)	35,5 (10,3)	42 (15)	42,9 (10,6)
Mean disease duration (months, SD)	112 (157)	120 (167)	84,6 (73,9)	108 (173)
Previous NORB	22 (38,2%) pts	17 (50%) pts	2 (25%) pts	3 (20%) pts

Figure 1. OCT RNFL in temporal zone in subgroups



Firstly, we analyze the impact of NORB on OCT and OCT-A. Our findings are consistent with literature data indicating that, in cases with previous NORB, there is a thinning of the RNFL (in the temporal, superior, and nasal sectors) and a reduction in GCC thickness (both in the superior and inferior regions). Concurrently, OCT-A didn't reveal significant differences in vessel density between eyes with history of optic neuritis and unaffected eyes. Structural OCT in three subgroups revealed a thickness reduction of the RNFL in the temporal zone in MS compared to MSplus/nMS (**Figure 1**). Addictionally, a reduction of the vascular plexus density was observed in both the superficial and deep capillary plexuses (inner and outer zones) in MSplus/nMS compared to MS (**Figure 2**). Within the CVS group analysis, the retinal vessel density in the inner and outer zones of both the superficial and deep capillary plexuses was remarkably reduced in CVS- compared to CVS+ (**Figure 3 and 4**).

Figure 2.1 Superficial (SCP) vessel density of different zones in subgroups

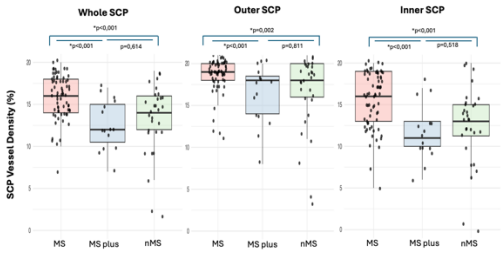


Figure 2.2 Deep (DCP) vessel density of different zones in subgroups

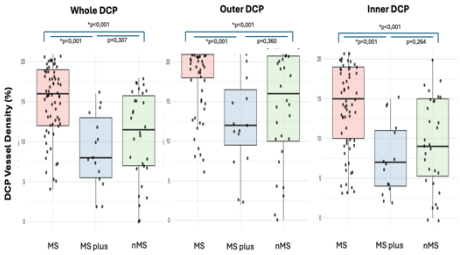


Figure 3. PVL distribution in MS, MSplus and nMS

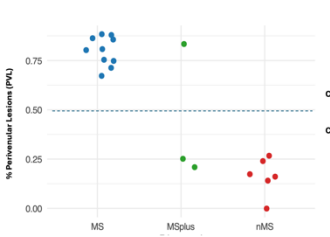
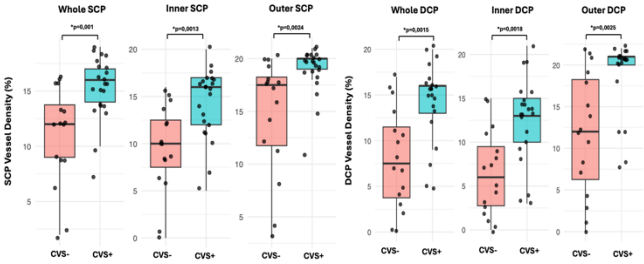


Figure 4. Superficial (SCP) and Deep (DCP) Capillary Plexus vessel density in CVS+ and CVS-



Conclusions

Compared to MS, MSplus and nMS exhibited reduced macular perfusion despite the absence of structural retinal damage, suggesting primary microvascular involvement. Ongoing studies aim to validate ophthalmological imaging as a reliable tool for early differential diagnosis among MS-like syndromes and to characterize the potentially non-demyelinating pathogenic mechanisms underlying these conditions.