Neurodegeneration and demyelination along the visual pathway are more prominent in secondary progressive than primary progressive multiple sclerosis

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Introduction

Progressive multiple sclerosis is receiving increasing attentions in the last years for its still unmet therapeutic need; in this work we investigated some pathophysiologic aspects of progressive MS focusing on the visual pathway to outline possible differences between different categories of progressive patients. In recent years, thanks to technological innovations, the visual pathway is receiving infact increasing attentions as a reliable model to study central nervous system damage in vivo and in a non-invasive way [1]. In particular optical coherence tomography (OCT) can be used to measure retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thickness as a marker of axonal and neuronal loss allowing to detect neurodegeneration [2]; on the other hand traditional visual evoked potentials (VEPs) can be performed as an indicator of demyelination [3].
There is little specific information about VEPs in progressive MS because the majority of the studies were performed prior to the current division of progressive and relapsing onset; available data suggest high percentages of visual conduction impairment in both primary (PP) and secondary progressive (SP) MS patients [4,5]. OCT studies evidence decreased RNFL thickness in progressive MS patients compared to controls [6]; with morphological damage apparently more prominent among SPMS than PPMS patients [7, 8]. In the present study we wanted to combine functional and morphological exploration of the visual pathway in order to underline possible pathophysiologic differences between PPMS and SPMS in terms of structure-function relation.

Methods

One hundred progressive MS patients (55 SP, 45 PP - clinical and demographic data reported in ***Table 1***) and 42 healthy controls (HC) were examined cross-sectionally with visual acuity (VA) test, full-field pattern-reversal VEPs and OCT. Patients with ophthalmological comorbidities were not enrolled in the study. OCT was performed using a high-resolution spectral-domain device (Heidelberg Spectralis-OCT: Spectralis; Heidelberg Engineering, Heidelberg, Germany); RNFL was measured with a 3.5 mm standard circle scan protocol centered on the optic disc, inner and outer boundaries were automatically identified by a segmentation algorhythm provided by the constructor and thickness was interpreted using a dataset of normal values, normalized according to age and sex, provided by the constructor. Mean GCL/IPL thickness was measured using a built-in Fast Macular Volume protocol consisting in 25 B-scans vertically crossing the macula. VEPs were performed using a pattern reversal stimulus on a LCD monitor at three different check-size (60', 30' and 15'), with a single recording channel (2 electrodes at Oz and Cz of the international 10-20 system); for each check-size at least three tracks were acquired in order to grant proper reproducibility of recorded cortical responses. Exams were interpreted as normal / abnormal according to our neurophysiology lab latency and amplitude normative data. VA was tested assessing both High-Contrast visual acuity (HCVA) and Low-Contrast Letter Acuity (LCLA) measured at the time of OCT/VEPs examination using a retro-illuminated high (100%) and 2.5% low Contrast Sloan Letter Charts (Precision Vision, LaSalle, IL).

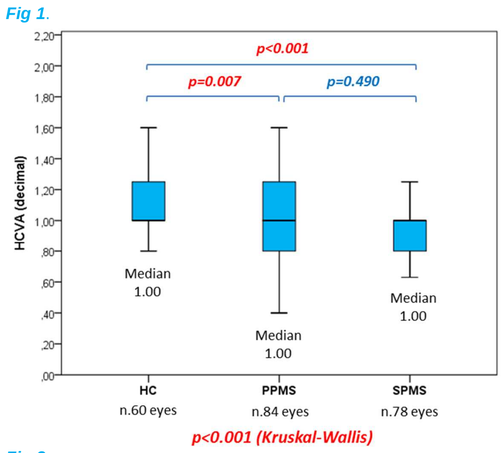
	SPMS (n.55)	PPMS (n.45)	HC (n.42)	Sig.
Age (mean)	47.9±8.8 years	51.4±8.1 years	40.4±16.6 years	p=0.052
Sex (Female/Male)	39/16	25/20	33/9	p=0.113
Disease Duration (mean)	20.0±7.6 years	8.4±4.6 years	-	p<0.001
Progression Duration (mean)	7.4±4.1 years	8.4±4.6 years	-	p=0.284
EDSS (median)	6.0 (2.5-7.5)	6.0 (2.0-7.0)	-	p=0.538
ON eyes	32/110 (7 bilateral)	2/90	-	-

Table 1. Clinical and Demographic data.

Results

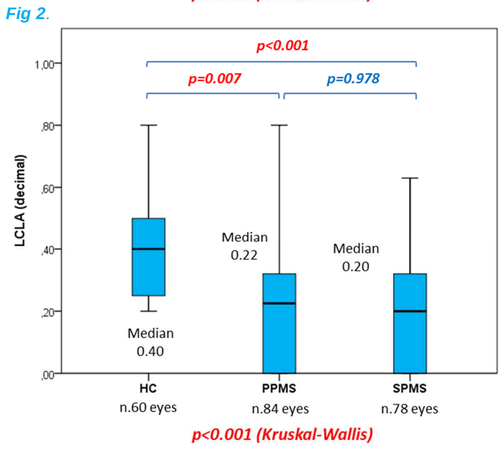
We compared clincal and instrumental measures in PPMS, SPMS and HC: ***Visual acuity*** - after excluding eyes with previous ON, despite similar median values (1.00 decimals in all subgroups), HCVA distribution resulted significantly lower than in HC both in PPMS (p=0.007) and SPMS patients (p<0.001) with no significant difference in terms of distribution between the two MS subgroups (p=0.490) [*Fig. 1*]. Similar results were found for LCLA (median values: HC 0.40, PPMS 0.22, SPMS 0.20; group distribution comparison; HC vs PPMS p<0.001, HC vs SPMS p<0.001, PPMS vs SPMS p=0.978) [*Fig. 2*]. ***VEPs-OCT alteration rate*** - independently from ON history VEPs showed similar rates of abnormality in the two subgroups (73.3% in PPMS vs 81.2% in SPMS, p=0.366), OCT abnormality was significantly more common among SPMS patients (35.5% in PPMS vs 66.6% in SPMS, p=0.002). Furthermore, when comparing the two techniques, VEPs percentage of abnormality was significantly higher than OCT in PPMS independently from ON history (p<0.001); this was also found in SPMS only after ON exclusion (p=0.033) [*Fig. 3*]. ***RNFL and GCC thickness*** - independently from previous ON, RNFL was found significantly reduced in both subgroups when compared with HC (mean 96.9 μm vs 88.9 μm, p=0.001 for PPMS; mean 96.9 μm vs 81.9 μm, p<0.001 for SPMS) with SPMS patients showing significantly lower values than PPMS patients (p=0.014) [*Fig. 4*]. Similar results were found when measuring ganglion cell complex (GCC) thickness on macular scans [*Fig. 5*]. ***VEPs latency*** - mean binocular VEPs latency was found to be significantly delayed in SPMS patients in comparison to both controls and PPMS patients, independently from previous ON [*Fig. 6*]. ***VEPs-OCT correlation*** - we found a strong significant inverse correlation between VEPs latency and RNFL-GCC (r= -0.611, p<0.001 for RNFL; r= -0.726, p<0.001 for GCC) in SPMS patients; we did not find any significant correlation when considering PPMS (r= -0.210, p=0.187 for RNFL; r= -0.270, p=0.085 for GCC) [*Fig. 7-8*].

Fig 1.



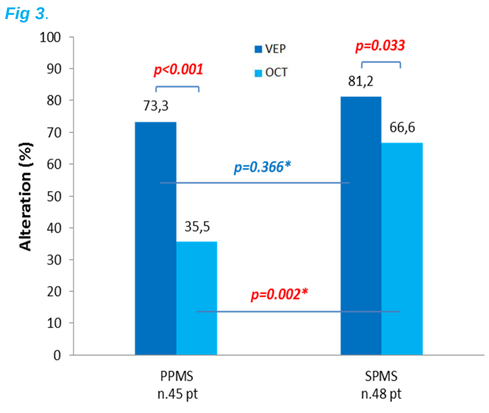
p<0.001 (Kruskal-Wallis)

Fig 2.



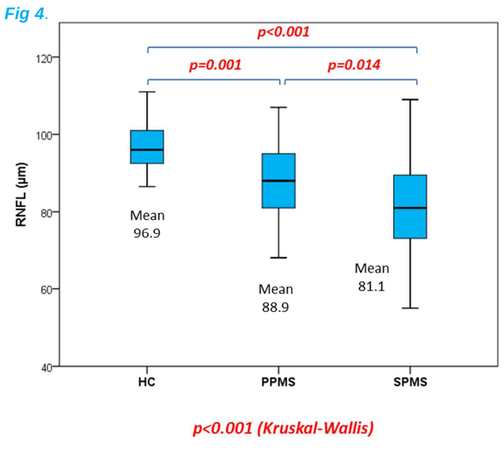
p<0.001 (Kruskal-Wallis)

Fig 3.



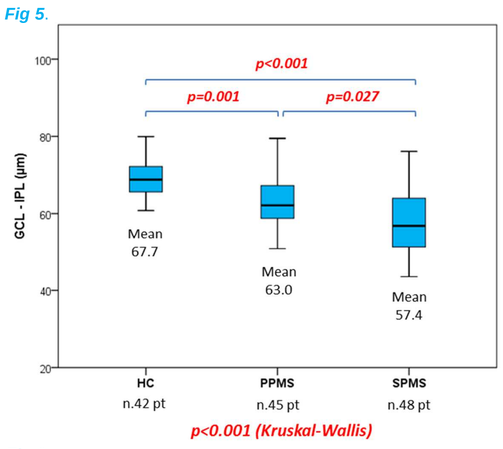
*(McNemar - *Mann-Whitney)*

Fig 4.



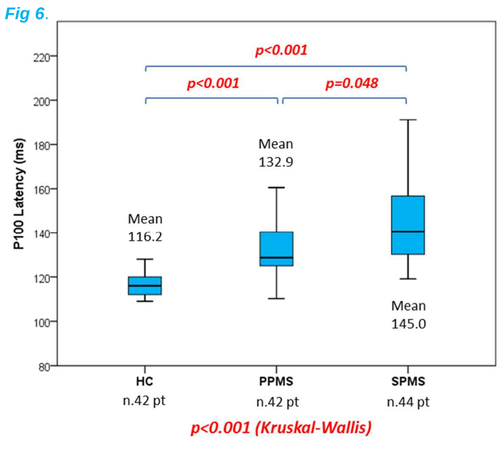
p<0.001 (Kruskal-Wallis)

Fig 5.



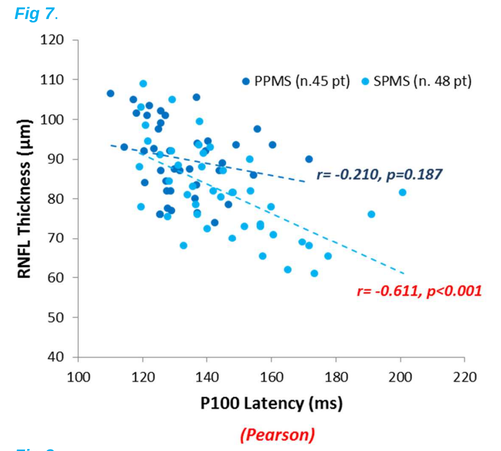
p<0.001 (Kruskal-Wallis)

Fig 6.



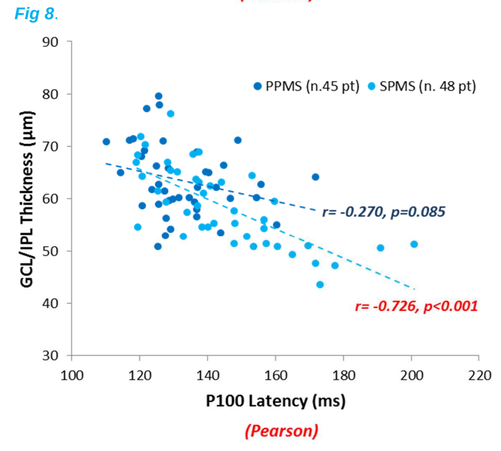
p<0.001 (Kruskal-Wallis)

Fig 7.



(Pearson)

Fig 8.



(Pearson)

Discussion and Conclusions

In eyes without previous optic neuritis, VEPs were more sensitive than OCT in detecting subclinical abnormalities, consistently with previous works using spectral-domain OCT devices [9]. Despite a similar frequency of VEPs abnormality in PPMS and SPMS [4], VEPs were more severely delayed in SPMS, independently from previous ON history. SPMS also had more frequent and severe RNFL/GCL thinning compared with PPMS, consistently with previous findings [7, 8]. In SPMS the severity of neuroaxonal thinning was significantly correlated with the severity of VEPs delay, while PPMS had a relatively homogeneous distribution of low/moderate abnormalities. In conclusion our findings suggest a more extensive demyelination, with associated neurodegeneration, along the visual pathway in SPMS compared with PPMS patients, independently from the previous occurrence of ON.

Bibliography and Acknowledgements

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