Visual pathway damage evolution in multiple sclerosis related acute optic neuritis

S. Guerrieri[1,2], M. Pisa[1,2], F. Sangalli[3], V. Martinelli[3], G. Comi[2,4], L. Leocani[1,2]

[1] *Experimental Neurophysiology Unit, Institute of Experimental Neurology (INSPE), San Raffaele Hospital, Milan, Italy*
[2] *Vita-Salute San Raffaele University, Milan, Italy*
[3] *Inflammatory CNS disorders Unit, Institute of Experimental Neurology (INSPE), San Raffaele Hospital, Milan, Italy*
[4] *Casa di Cura del Policlinico, Milan, Italy*

Introduction

In the assessment of the visual pathway in multiple sclerosis (MS) and acute optic neuritis (aON), optical coherence tomography (OCT) is used to measure peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell layer (GCL) thickness as markers of axonal and neuronal loss, allowing to detect neurodegeneration in vivo and in a non-invasive way. On the other hand full-field visual evoked potentials (ff-VEPs) can be performed as an indicator of demyelination, with multifocal technique (mf-VEPs) also allowing to assess conduction along the central visual pathways for separate portions of the visual field. Several studies [1-3] tried to evaluate and characterize the evolution over time of functional and structural parameters after acute inflammatory events involving the opting nerve, with aON that has recently become an elective platform to test the effects of neuroprotective and remyelinating drugs with unsatisfying results [4-6]; furthermore current clinical protocol are mainly related to the diagnostic phase of aON [7], while clear monitoring indications are still lacking. With this work we applied functional and structural monitoring techniques in order to better define the timing of optic nerve damage occurring after aON in the context of relapsing-remitting MS (RRMS) or clinically isolated syndrome (CIS); we also evaluated the role of mf-VEPs as an additional technique to monitor conduction along the visual pathway.

Methods

We performed a prospective longitudinal study [*Fig. 1*] enrolling 40 patients (16 CIS, 24 RRMS; mean age 29.9 ± 10.8 years) affected by aON who underwent a baseline clinical (High- HC and Low Contrast-LC visual acuity-VA test) and neurophysiological assessment (comprehensive of OCT and VEPs, both ff-VEPs and mf-VEPs) 4 weeks after clinical onset. A complete clinical and instrumental follow-up with VA test, OCT and VEPs was repeated at 3, 6 and 9 months. For 21 patients a pre-baseline assessment in the acute diagnostic phase was also available. ***VA*** was assessed using HCVA and LCVA retro-illuminated Sloan Letter Charts. ***OCT*** was performed using a high-resolution spectral-domain device (Heidelberg Spectralis™): peripapillary retinal nerve fiber layer (pRNFL) thickness was measured on a standard 12° circle scan around the optic disc, ganglion cell layer (GCL) was measured (combined with inner plexiform layer-IPL) using a fast macular volume protocol scan vertically crossing the macula, this scan was also used to measure macular RNFL (mRNFL) and other retinal layers; follow-up scans were acquired using the AutoRescan™ software provided by the producer in order to maximize reproducibility. ***Full-field VEPs*** (ff-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. ***Multifocal VEPs*** (mf-VEPs) were performed using a 56-segments dartboard pattern on a LCD monitor with 2 recording occipital channels (horizontal and vertical) with each segment giving an independent stimulus controlled by Terra™ software performing a Fast Fourier analysis of all raw signals and extracting VEP response from the continuous basal EEG. For each segment latency of the second peak was measured within the complex with the highest peak-to-peak amplitude. ***Statistical analysis*** were performed using IBM SPSSTM software (version 25.0): Within-subjects differences over time have been assessed using a general linear model (repeated-measures ANOVA) or non-parametric Friedman's test, according to variables distribution. Correlations between study measures have been assessed using Pearson or Spearman coefficients, according to variable type (linear or categorical respectively); simple and multiple linear regression models have been also applied to investigate possible relations between functional and structural parameters. Finally the sensitivity of our study techniques has been compared using a Cochran Q model.

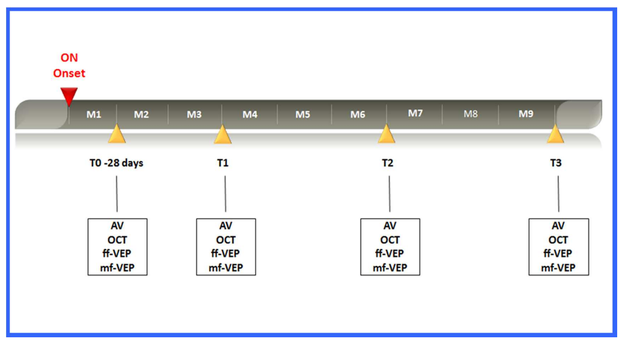


Figure 1. ***Study Design.***

Results

VEPs latency was initially delayed (mean: 135.5 ms for ff-VEP; 169.1 ms for mf-VEP) to progressively recover over months 1-9 (mean change: -9.94 ms, p<0.001 for ff-VEPs; -9.0 ms, p=0.001 for mf-VEPs) [*Table 1*] , with a parallel peripapillary retinal nerve fiber layer (pRNFL) thinning (mean change: -9.8 µm, p<0.001). Ganglion cell - inner plexiform layer (GCIPL) and macular RNFL (mRNFL) thinning were already detectable within the first month, together with inner (INL) and outer nuclear layer (ONL) thickening [*Table 2*]. Pre-baseline ff-VEPs latency (Adj.R^2=0.153, β - 0.445, p=0.049) and GCIPL thinning at 1 month (Adj.R^2=0.647, β 0.815, p<0.001) predicted subsequent pRNFL loss [*Fig. 2*]. Initial ff-VEPs latency ≥140 ms was associated with pRNFL loss >5 µm (χ^2 5.79, p=0.016); the same outcome was found in patients aged >33 years with ff-VEPs latency <140 ms (χ^2 3.309, p=0.049) [*Fig. 3*]. At 1 month ff-VEPs and mf-VEPs abnormality rates did not differ significantly (77% vs 85%, p=0.998), both performing better than OCT (42%, p<0.001); at 9 months mf-VEPs were more sensitive than ff-VEPs (65% vs 40%, p=0.035) [*Fig. 4*].

Tab. 1

	Timepoints[a]		*p value*	*Timepoints*[b]				*p value*						
	Acute	Month 1	Ac - m 1	Month 1	Month 3	Month 6	Month 9	global	m 1-3	m 1-6	m 1-9	m 3-6	m 3-9	m 6-9
ff-VEPs Latency	138.68 (128.90 - 149.96)	133.56 (119.60 - 140.51)	0.020*	135.45 (128.28 - 145.79)	131,2 (125.16 - 141.99)	130.71 (123.90 - 138.21)	126.94 (120.93 - 133.06)	<0.001*	0.272	0.039*	<0.001*	1.000	0.001*	0.014*
ff-VEPs Amplitude	4.59 (3.26 - 5.92)	10.12 (6.98 - 13.26)	0.005*	9.10 (7.17 - 11.68)	8.61 (6.65 - 11.23)	7.94 (5.99 - 10.23)	9.17 (6.67 - 11.35)	0.086	-	-	-	-	-	-
mf-VEPs Latency	171.80 (157.90 - 175.56)	163.33 (153.68 - 171.24)	0.015*	169.10 (161.04 - 174.87)	163.10 (155.48 - 167.05)	162.32 (154.90 - 164.78)	160.10 (153.40 - 163.50)	0.002*	0.045*	0.029*	0.001*	1.000	0.698	0.245
mf-VEPs Amplitude	89.90 (64.29 - 115.51)	135.23 (105.09 - 1654.38)	0.001*	116.67 (99.04 - 148.56)	137.42 (120.57 - 166.80)	137.78 (119.74 - 166.10)	142.64 (124.93 - 171.99)	0.001*	0.026*	0.020*	0.017*	1.000	1.000	1.000

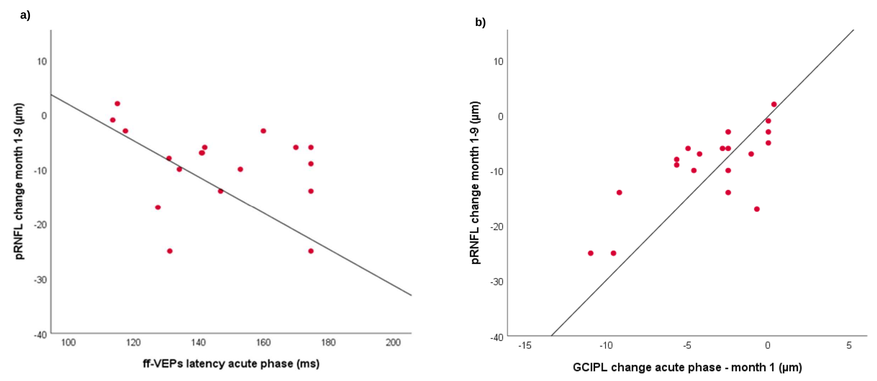
VEPs parameters (mean and 95% Confidence Interval) evolution in aON eyes within the 1st month (*Timepoints*[a], n=16 for ff-VEPs and n=21 for mf-VEPs - 5 eyes had no recordable ff-VEPs cortical responses) and at 1, 3, 6 and 9 months (*Timepoints*[b], n=37 for ff-VEPs and n=40 for mf-VEPs - 3 eyes had no recordable ff-VEPs cortical responses) after ON onset. Within-subjects differences over time (p value) have been assessed using a general linear model (repeated-measures ANOVA) or non-parametric Friedman's test, according to variables distribution. Bonferroni correction has been applied for multiple comparisons, significant results are highlighted (*).

Tab. 2

	Timepoints[a]		*p value*	*Timepoints*[b]				*p value*						
	Acute	Month 1	Ac - m 1	Month 1	Month 3	Month 6	Month 9	global	m 1-3	m 1-6	m 1-9	m 3-6	m 3-9	m 6-9
pRNFL (global)	98.23 (90.84 - 105.63)	96.66 (90.59 - 102.74)	0.467	95.67 (89.90 - 101.44)	87.97 (82.18 - 93.75)	85.82 (79.83 - 91.80)	85.88 (79.84 - 91.90)	<0.001*	0.002*	<0.001*	<0.001*	<0.001*	<0.001*	1.000
pRNFL (temporal)	69.04 (63.01 - 75.79)	66.33 (60.59 - 72.06)	0.065	61.70 (56.61 - 66.79)	53.64 (48.65 - 58.64)	52.88 (47.78 - 57.97)	52.32 (47.04 - 57.60)	0.004*	0.002*	0.002*	0.002*	0.788	0.433	1.000
pRNFL (PMB)	51.71 (46.93 - 56.49)	48.42 (43.26 - 53.59)	0.001*	45.50 (41.94 - 49.05)	40.50 (36.62 - 44.38)	40.61 (36.83 - 44.39)	40.00 (36.18 - 43.60)	0.006*	0.006*	0.012*	0.005*	1.000	1.000	1.000
mRNFL	33.32 (31.45 - 35.19)	32.51 (30.39 - 34.63)	0.048*	30.91 (29.10 - 32.72)	28.83 (26.83 - 30.82)	29.14 (27.05 - 31.22)	28.76 (26.79 - 30.74)	<0.001*	0.003*	0.021*	<0.001*	0.962	1.000	1.000
GCIPL	68.65 (65.76 - 71.55)	64.59 (61.35 - 67.83)	<0.001*	62.73 (59.97 - 65.48)	61.99 (58.87 - 65.10)	62.36 (59.35 - 65.38)	61.42 (57.67 - 65.16)	0.352	-	-	-	-	-	-
INL	34.42 (33.11 - 35.72)	35.35 (34.27 - 36.42)	0.029*	34.71 (33.93 - 35.49)	34.39 (33.59 - 35.18)	34.38 (33.61 - 35.16)	34.61 (33.62 - 35.61)	0.179	-	-	-	-	-	-
OPL	28.87 (27.67 - 30.07)	29.34 (28.18 - 30.51)	0.450	29.13 (28.28 - 29.97)	29.21 (28.51 - 29.91)	28.70 (27.98 - 29.42)	28.98 (28.16 - 29.80)	0.257	-	-	-	-	-	-
ONL	62.20 (59.09 - 65.31)	64.52 (61.57 - 67.48)	0.002*	63.23 (61.22 - 65.23)	62.28 (60.41 - 64.14)	62.10 (60.28 - 63.92)	61.49 (59.76 - 63.21)	0.001*	0.199	0.061	0.004*	1.000	0.342	0.713
RPE	14.71 (14.02 - 15.41)	14.76 (14.14 - 15.38)	0.773	14.75 (14.28 - 15.22)	14.91 (14.44 - 15.23)	14.97 (14.52 - 15.41)	14.80 (14.39 - 15.21)	0.290	-	-	-	-	-	-

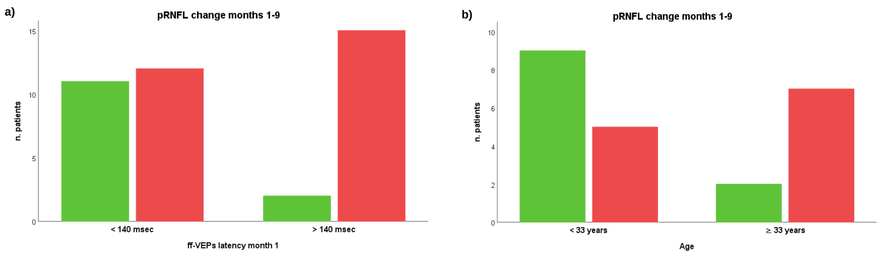
RNFL parameters (mean and 95% Confidence Interval) evolution in aON eyes within the 1st month (*Timepoints*[a], n=21) and at 1, 3, 6 and 9 months (*Timepoints*[b], n=40) after ON onset. Within-subjects differences over time (*p value*) have been assessed using a general linear model (repeated-measures ANOVA) or non-parametric Friedman's test, according to variables distribution. Bonferroni correction has been applied for multiple comparisons, significant results are highlighted (*).

Fig. 2



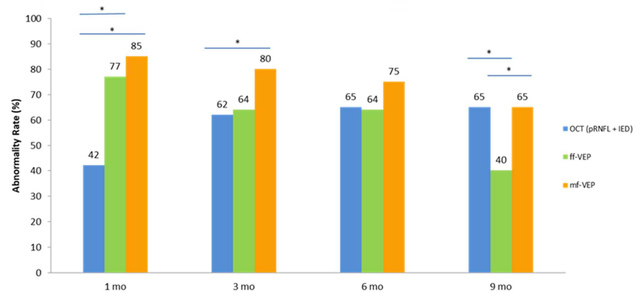
a) Linear regression model between ff-VEPs latency in the acute phase (mean 4.7 days; range 1-9) and subsequent pRNFL thickness change over months 1 to 9 (R2=0.20, adj. R2=0.15, F=4.43, p=0.049) in aON eyes (n=21). **b**) Linear regression model between GCIPL change between the acute phase (mean 4.7 days; range 1-9) and month 1 and subsequent pRNFL thickness change over months 1 to 9 (R2=0.66, adj. R2=0.65, F=37.58, p<0.001) in aON eyes (n=21).

Fig. 3



a) VEPs latency >140 ms at 1 month was significantly associated with µm pRNFL loss >5 µm (χ2 5.79, p=0.016). **b**) In patients with VEPs latency of less than 140 ms at 1 month, age ≥33 years was associated with the same outcome (χ2 3.309, p=0.049).

Fig. 4



OCT, ff-VEPs and mf-VEPs abnormality rates from months 1 to 9 in 40 aON eyes. For each timepoint the sensitivity of the three techniques has been compared using a Cochran Q model, Bonferroni correction has been applied for multiple comparisons (significant results are highlighted *).

Discussion and Conclusions

Our results suggest ***significant retinal damage has already occurred within the 1st month after aON*** with the extent of initial ***demyelination and age*** influencing the degree of consequent neurodegeneration; ***hyperacute recruitment*** is therefore crucial to prompt remyelinating and neuroprotective strategies. Considering their ability to maintain sensitivity over time, we suggest ***mf-VEPs inclusion among aON monitoring and interventional protocols***.

Bibliography and Acknowledgements

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