VISUAL EVOKED POTENTIALS AND OPTICAL COHERENCE TOMOGRAPHY TO DETECT OPTIC NEURITIS IN C57BL/6

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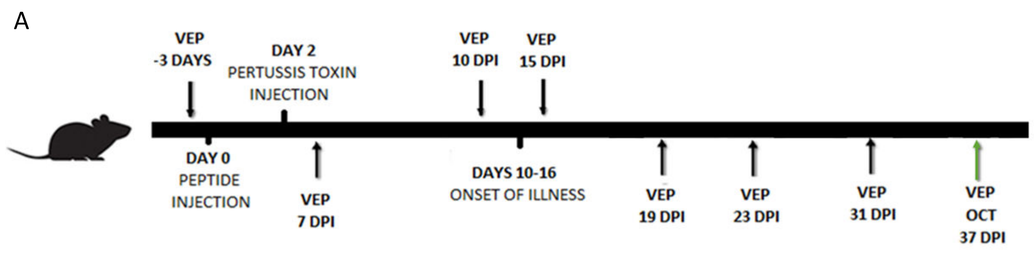
Introduction

Background: Multiple sclerosis (MS) is a disease of the central nervous system in which the interplay between inflammatory and neurodegenerative processes typically results in intermittent neurological disorders followed by progressive accumulation of disability[1]. The first clinical symptom observed in about 26% of relapsing-remitting and secondary progressive MS patients is optic neuritis (ON). ON is an acute inflammatory disorder that causes demyelination of the optic nerve, thinning of the retinal nerve fiber layer (RNFL), and death of retinal ganglion cells (RGCs)[2]. These clinical symptoms can be observed and studied in the experimental autoimmune encephalomyelitis (EAE) model induced through myelin oligodendrocyte glycoprotein (MOG) injection[3]. Immunized C57BL/6 mice develop chronic EAE[4]. For what concerns the visual system, EAE is characterized by optic nerve abnormalities, consisting in demyelination and/or axonal loss, and retina damage detectable with visual evoked potentials (VEPs) and optical coherence tomography (OCT)[5] respectively.

Objective: The present study aims at investigating the usefulness of non-invasive visual evoked potential (VEP) and optical coherence tomography (OCT) to detect optic nerve involvement in the EAE model.

Results

Clinical score, VEP latency and OCT



Representative VEP traces

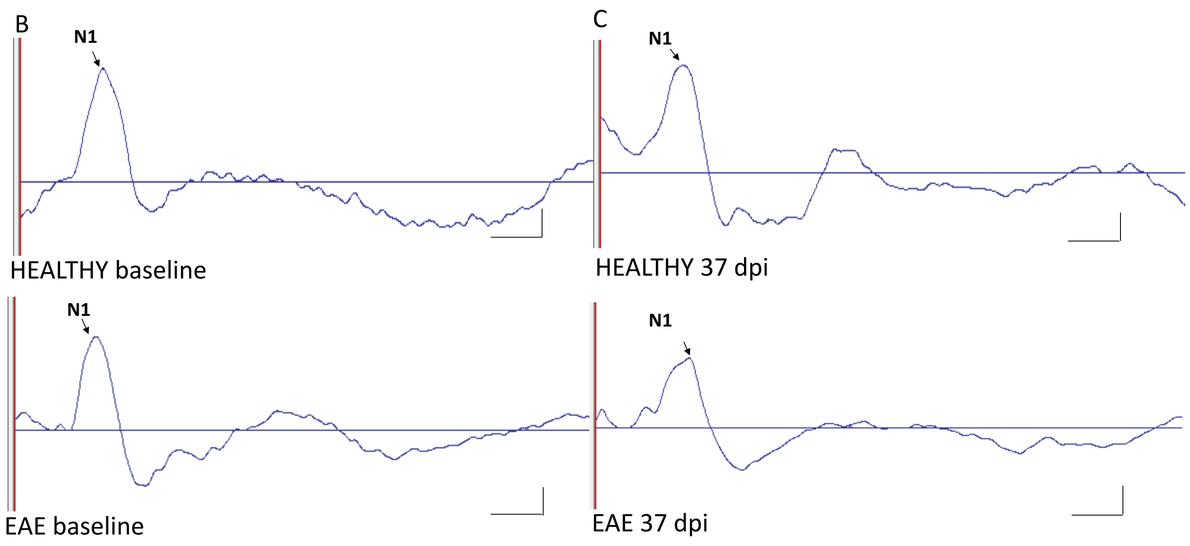


Figure 1. A. Experimental timeline from -3 to 37 days post immunization (dpi). B. Example of HEALTHY and EAE VEP traces at the baseline. C. Example of HEALTHY and EAE VEP traces at 37 dpi. Horizontal bar: 50 ms; vertical bar: 50 µV.

Clinical score

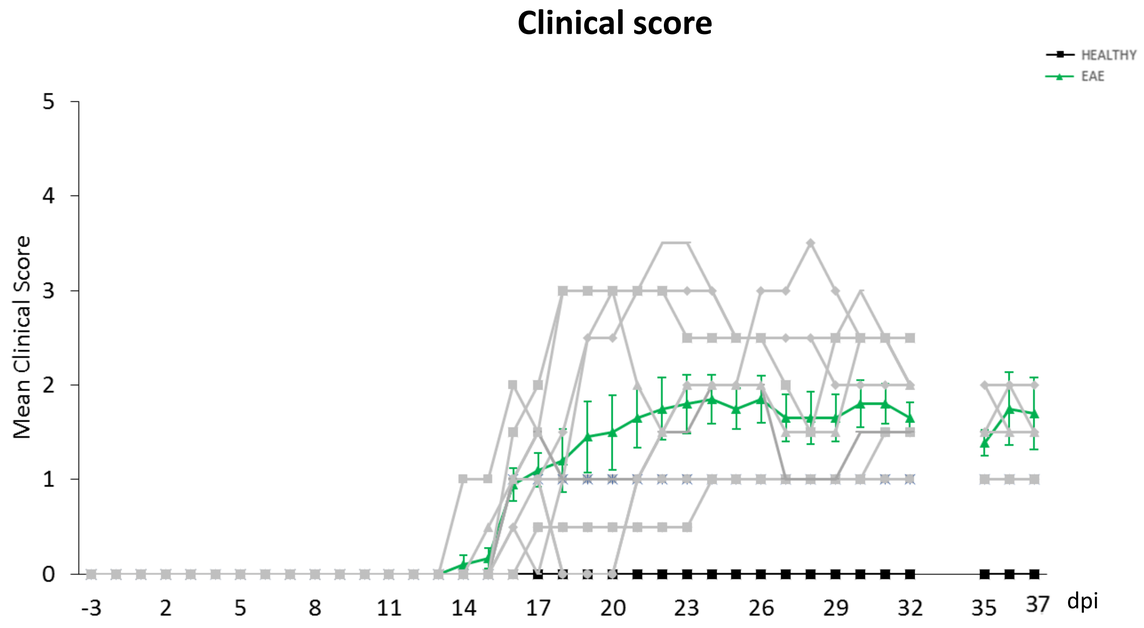


Figure 2. Disease course of EAE. Grey lines represent the individual curves of 10 EAE mice, while the green line depicts the mean (±SEM) of the EAE group. Black line represents the HEALTHY group. The onset was observed at 16 dpi. The correlation between clinical score and latency (ms) was not significant (r=0.161; p=0.511).

EAE clinical symptoms started at 16 dpi. The EAE latency was significantly increased at 11 (p=0.026) and 15 (p=0.041) dpi, hence preceding the motor disability, and continued to be significantly increased after the clinical onset: at 19 (p=0.001), 31 (p=0.021) and 37 dpi (p<0.0001), with partial recovery at 23 dpi (p=0.195) (Fig. 3). While the amplitude was significantly decreased only at 31 dpi (p=0.006) (Fig. 4). OCT showed a significant decrease in 5 of 7 EAE eyes (upper cutoff value=69.68 µm; lower cutoff value=63.42 µm. Fig. 6). The correlation between VEP latency (ms) and NGCC thickness was significant at 37 dpi (p=0.007) (Fig. 7).

VEP latency

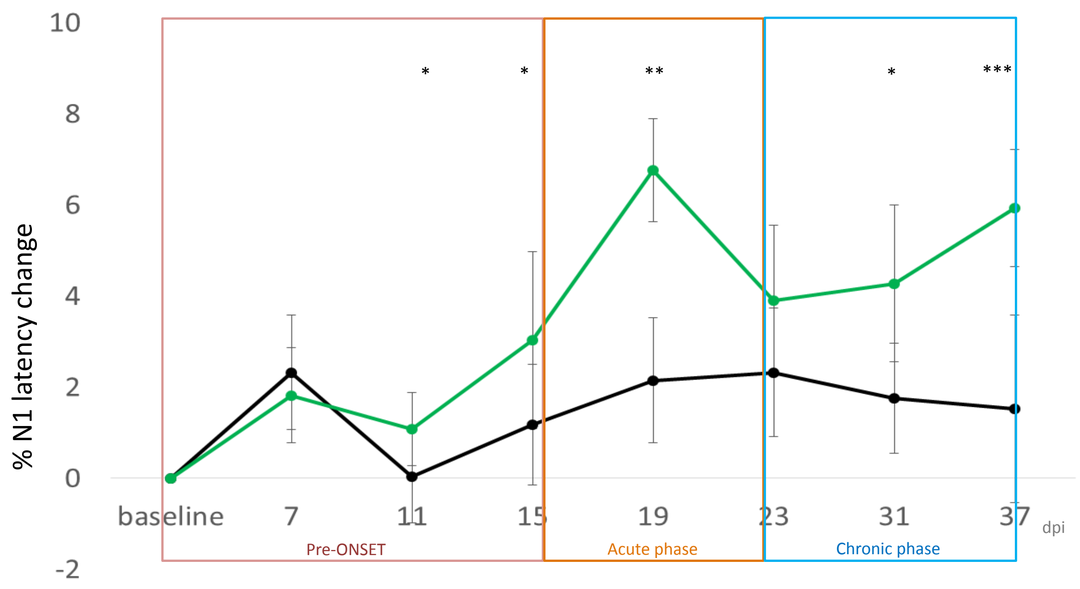


Figure 3. Percentage of N1 latency change in EAE (green line, n=10) and HEALTHY group (black line, n=7) normalized on baseline. The error bars represent the SEM. Statistically significant differences between EAE and HEALTHY group were detected at 11, 15, 19, 31 and 37 dpi.

VEP amplitude

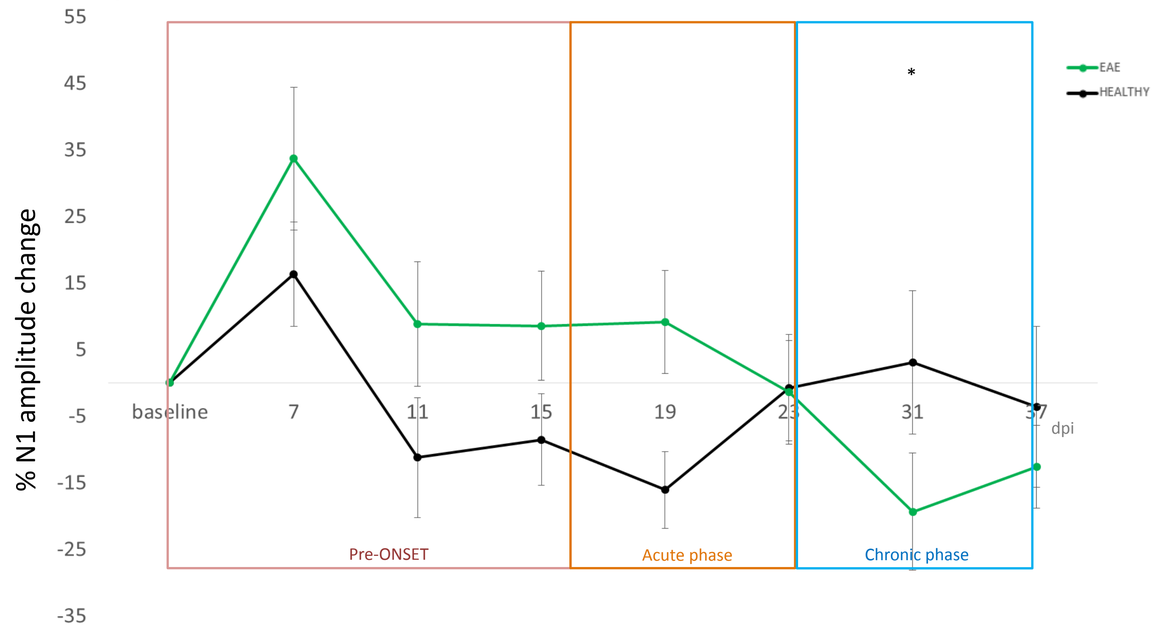


Figure 4. Percentage of N1 amplitude change in EAE (green line, n=10) and HEALTHY group (black line, n=7) normalized on baseline. The error bars represent the SEM. Statistically significant difference between EAE and HEALTHY group were detected at 31 dpi.

Segmentation mouse retina layers

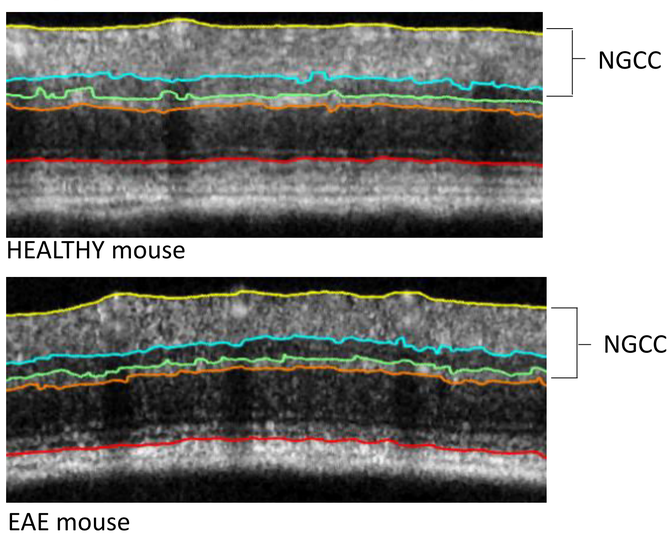


Figure 5. Examples of OCT segmentation in HEALTHY and EAE mice at 37 dpi. Neuronal ganglion cells complex (NGCC) consists of retina nerve fiber layer (RNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL).

NGCC thickness

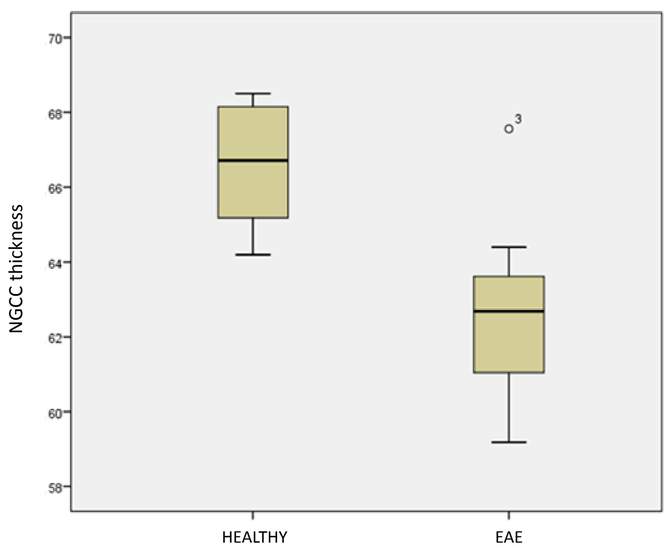


Figure 6. NGCC thickenss in HEALTHY and EAE mice at 37 dpi. Significant reduction was observed in EAE mice (p=0.008; EAE=7 eyes and HEALTHY=7 eyes).

Latency and NGCC thickness correlation

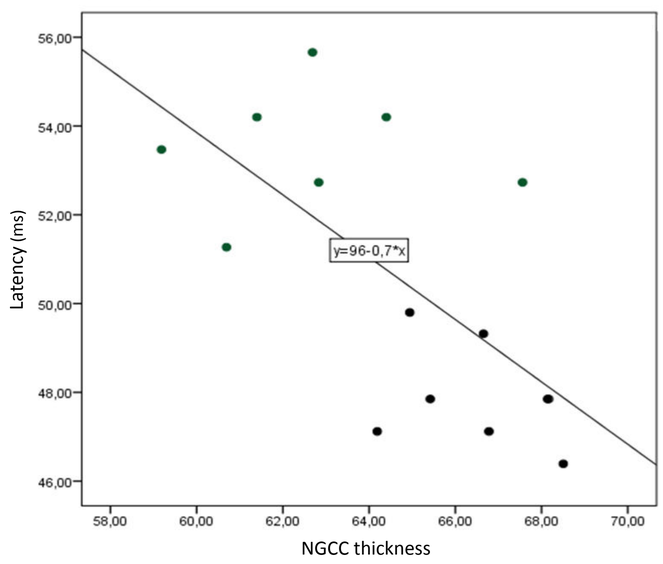


Figure 7. Significant Pearson's correlation between VEP latency and NGCC thikness was found at 37 dpi (r=-0,661; p=0.007). Green dots represent EAE (7 eyes) and black dots represent HEALTHY (7 eyes).

Discussion

✓N1 latencies of EAE mice were significantly delayed, compared with the healthy group, before the clinical onset (at 11 and 15 dpi), as well as after the onset (at 19, 31 and 37 dpi). The partial recovery observed at 23 dpi could be due to an increase of the healthy group latency. The amplitude showed a greater variability compared to the latency, but a significant difference between EAE and HEALTHY group could be observed in the chronic phase.

✓OCT showed a significant reduction of NGCC thickness in EAE compared to healthy group at 37 dpi. The correlation between latency delay and NGCC thickness was significant.

✓The results suggest that inflammation probably influences the latency in the pre-ONSET phase, while subsequently there is myelin degeneration and, in the chronic phase, axon degeneration.

✓These findings suggest that VEPs can be used as an early biomarker of demyelination in EAE to test new remyelinating treatments, while OCT is suitable for monitoring subsequent neuroaxonal loss for testing neuroprotective strategies.

Literature

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Conflict of interest

The authors declare no competing financial interest.

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