Title: Visual pathway damage evolution in multiple sclerosis related acute optic neuritis.

Short title: Visual pathway damage in MS-aON.

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Background and Aims: full-field visual evoked potentials (ff-VEPs) and optical coherence tomography (OCT) are used to monitor acute optic neuritis (aON), to assess demyelination and neurodegeneration. Multifocal VEPs (mf-VEPs) allow the topographic characterization of optic nerve damage. We explored the value of these techniques in describing the functional and structural damage after aON in relapsing-remitting multiple sclerosis (RRMS) or clinically isolated syndrome (CIS).

Methods: prospective study enrolling 16 CIS and 24 RRMS patients with a first aON episode in the study eye, who underwent OCT, ff-VEPs and mf-VEPs at 4 weeks after onset, with follow-up at 3, 6 and 9 months. For 21 patients pre-baseline assessment was available.

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), with a parallel peripapillary retinal nerve fiber layer (pRNFL) thinning (mean change: -9.8 µm, $p<0.001$). Ganglion cell-inner plexiform layer (GCIPL) atrophy was already detectable at 1 month. Pre-baseline ff-VEPs latency (Adj.R2=0.153, β -0.445, $p=0.049$) and GCIPL thinning at 1 month (Adj.R2=0.647, β 0.815, $p<0.001$) predicted subsequent pRNFL loss. Initial ff-VEPs latency ≥140 ms was associated with pRNFL loss >5 µm ($\chi2$ 5.79, $p=0.016$); the same outcome was found in patients aged >33 years with ff-VEPs latency <140 ms ($\chi2$ 3.309, $p=0.049$). 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%, $p=0.035$).

Conclusions: significant retinal damage has occurred within 1 month after aON, with initial demyelination and age influencing consequent neurodegeneration; hyperacute recruitment is therefore crucial to prompt remyelinating and neuroprotective strategies. Considering their sensitivity over time, we suggest mf-VEPs inclusion among aON monitoring protocols.

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