• Brief Report •

Mechanism of delayed conduction of fellow eyes in patients with optic neuritis

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Abstract

• To test the hypothesis that latency delay in the fellow eyes of optic neuritis (ON) patients and to compensate for delayed transmission of visual information, latency change of multi-focal visual evoked potential (mfVEP) traces in fellow eyes of 15 ON patients were analyzed. Patients with low risk (LR) for developing multiple sclerosis (MS) were examined separately from MS patients to isolate effect of cortical plasticity from potential pathological changes in disseminated disease. The small increase in latency in fellow eyes of LR group was statistically not significant. In MS patients, the latency was significantly delayed (P<0.02). The magnitude of the latency change in the fellow eyes did not correlate with the severity of latency delay in the affected eyes (R^2<0.02, P=0.3). The differences between ON patients with and without MS, reported here, suggest that the presence of disseminated disease plays critical role in latency delay of the fellow eye.

• **KEYWORDS:** multi-focal visual evoked potential; optic neuritis; fellow eyes; latency delay

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INTRODUCTION

Optic neuritis (ON) is a common form of inflammatory demyelination. It is often associated with multiple sclerosis (MS) and is the presenting symptom in approximately 20% of MS patients[1]. However in a significant proportion of patients, ON remains a single demyelinating episode of unknown etiology.

In contrast with most demyelinating brain lesions, the effect of the disease on the optic nerve is clinically apparent and potentially quantifiable by various techniques[2]. The visual evoked potential (VEP) was developed as an objective functional assessment of the integrity of the visual pathway, and its use in ON is well documented[3]. Delayed conduction of the VEP in the affected eye has been found in the majority of patients with ON and is thought to reflect demyelination of the optic nerve fibres[3]. Significant VEP latency delay is also found in large proportion of MS patients with no history of ON[4-5].

An alteration of the VEP has been reported in the fellow eye of patients with ON in an absence of clinical symptoms[5-8]. These changes, of amplitude reduction and latency delay have been attributed to various factors including sub-clinical ON, inflammation spillover at the chiasm or retro-chiasmal pathology.

Recently, adaptive cortical plasticity has been suggested as an important factor that may contribute to latency delay in the fellow eye. It has been postulated that temporal reorganization at cortical level compensates for delayed transmission of visual information to improve binocular vision[9].

In the current study, we test this hypothesis by analyzing latency change of multi-focal VEP traces in fellow eyes of ON patients during first 12mo after the attack. Multifocal VEP provides a unique opportunity to evaluate locally induced responses, increasing, therefore, the technique sensitivity and improving its spatial resolution by eliminating waveform cancellation effect and including peripheral visual field segments[10].

In order to isolate effect of cortical plasticity from potential pathological changes that may occur in the visual system in disseminated disease, patients with ON and a normal magnetic resonace imaging (MRI) were examined separately from those with a diagnosis of MS.

METHODS

Subjects Patients presenting with a unilateral typical acute ON, as determined by a neuro-ophthalmologist, with no previous history of inflammatory demyelinating episodes were enrolled. Patients with an atypical ON presentation, clinical

involvement of the other eye or other ophthalmic conditions that could affect the multi-focal visual evoked potential (mfVEP) measurements were excluded. Patients had a brain and spine MRI within 2wk of the onset of ON and at least one follow up MRI within the next 12mo. A diagnosis of clinically definite multiple sclerosis (CDMS) was made by a neurology consultant based on revised McDonald Criteria for MS[11].

ON patients were analyzed as one group and then divided retrospectively on the bases of MS diagnosis into two subgroups: 1) ON with low risk (LR) of developing MS, patients had normal MRI brain and spine, with no inflammatory demyelination lesions, at least for the 12mo after attack; 2) MS group, ON with brain or spine inflammatory demyelinating lesions on MRI and later were diagnosed with CDMS. Eight age and gender controls were enrolled for comparison. All participants underwent visual acuity testing, ophthalmic evaluation, and were tested using mfVEP. Sydney University Ethics Committee approved the study and all procedures adhered to the tenets of the Declaration of Helsinki with informed consent obtained from all participants.

Multi-focal Visual Evoked Potential Recording and Analysis mfVEP testing was performed using Accumap (ObjectiVision Pty. Ltd., Sydney, Australia) as descried previously (Figure 1)[6].

All recordings were performed monocularly. Raw data were exported into Microsoft Excel format for analysis. Good signal to noise ratio (SNR) was calculated by dividing amplitude of signal by noise. Noise level was calculated as the standard deviation of amplitude between 400 to 800ms. Only traces with SNR>2 in both affected and fellow eyes at both sessions were included. Traces of 5/32 segments from 3 inner rings (eccentricity from 2 to 10 degrees) and 5/24 segments from two outer rings (eccentricity between 10 and 24 degrees) were randomly selected and analyzed at 3 and 12mo after attack in both affected and fellow eyes (Figure 1B). Of 5 inner segments and 5 outer segments in one randomly selected eye were analyzed for controls. The first and second major peaks between 70-200ms were recorded and analyzed (Figure 1C). Since 1st and 2nd peak latency of mfVEP is more reproducible than the onset of response, waveform width was evaluated by subtracting latency of 1st peak from the 2nd peak.

To test the assumption that a shift in latency and change in duration could be due to cortical adaptation, the correlation between latency delay of ON eyes and latency change of both peaks of fellow eyes were also evaluated. We predicted that patients with more latency delay in ON eyes would experience more delay in the fellow eye if the original hypothesis was true.

Statistical Analysis Statistical analysis was performed using SPSS 21.0 software. Paired Students' *t*-test was used to evaluate latency change between 3 and 12mo tests. One-way ANOVA-post Bonferroni correction was used to assess difference between groups. Spearman rank correlation and linear regression analysis were used to determine correlations between mfVEP values. A *P*-value of 0.05 or less was considered statistically significant

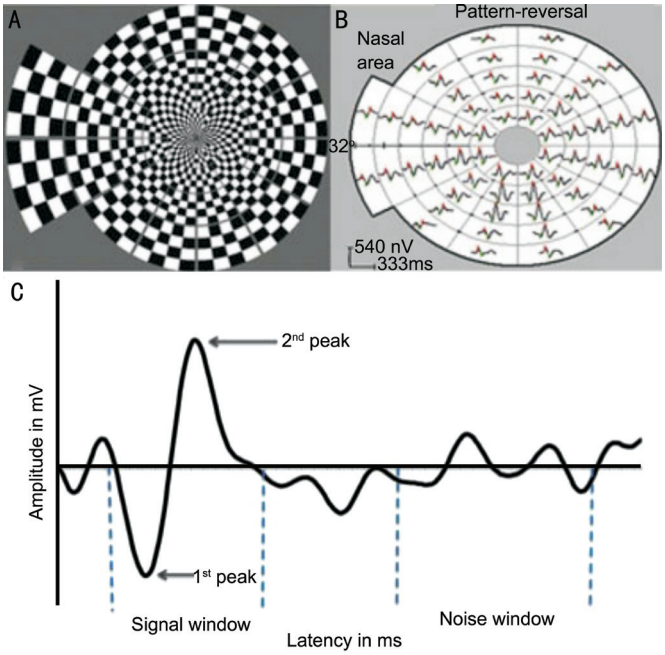

Figure 1 Cortically scaled reversed pattern visual stimuli with central fixating target (A), mfVEP traces of the right eye (B), and waveform of mfVEP recording illustrating 1st and 2nd peak locations used for analysis (C).

RESULTS AND DISCUSSION

Totally 15 acute ON patients were included, 7 patients had normal brain and spine MRIs and 8 patients were diagnosed with MS at a later stage. There was no significant difference in age or gender between groups. Total of 380 traces were analyzed (15 patients ×10 segments ×2 tests and 8 controls ×10 segments). Vertical channel recording constituted 57% of traces followed by horizontal channel 35%. Right and left oblique channels has <10% of total traces. The vertical channel has the best recording because the majority of visual fibers project to the upper bank of the sulcus calcarinus and the lower bank of the sulcus calcarinus. There was no significant difference between groups in regard to selected channels with *P*=0.66, controls had 1st peak latency of 95±10ms and 2nd peak latency of 140±14ms.

Subgroup Analysis When analyzing patients based on their diagnosis of either MS or LR, mfVEP traces of LR group showed small increase of latency of both peaks from 3 to 12mo (1.6±1.7ms and 1.7±3ms). The shift of first and second peak was similar (*P*=0.54). However, latency values still remained within normal range and there was no difference in both peaks compared to controls at both time points (Table 1).

Fellow Eye Latency in Optic Neuritis Patients At three months, mean latency of first and second peaks was significantly

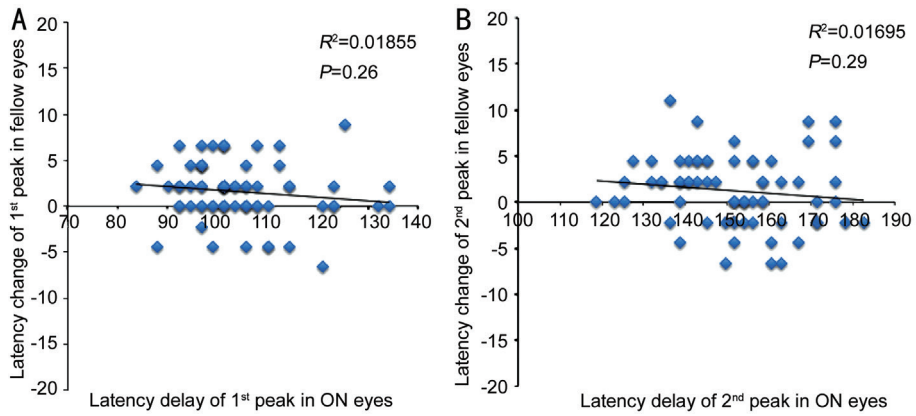

Figure 2 Linear regression plot between latency delay of 1st peak in ON eyes and change in latency delay of 1st peak in fellow eyes (A) and the latency delay of 2nd peak in ON eyes and change in latency delay of 2nd peak in fellow eyes (B) *R*-squared value and *P* value were included.

Table 1 Latency delay of 1st and 2nd peaks in fellow eyes compared to controls

Fellow eye (ms)	1st peak				2nd peak			
	3mo	[a]*P*	12mo	[a]*P*	3mo	[a]*P*	12mo	[a]*P*
Total	99.8±11.6	0.002	101.2±11	0.004	145.6±14	0.004	148±14.5	<0.001
LR	97±8.6	0.8	98.6±8.5	0.2	141.4±11	0.8	143.1±11.5	0.4
MS	102.2±13.3	<0.001	103.3±13	<0.001	149.2±15	<0.001	152.4±15.4	<0.001

[a]*P* value (one way-ANOVA post Bonferroni correction) compared to controls.

delayed in fellow eyes compared to controls (*P*=0.002 and 0.004 for first and second peak respectively).

Latency delay of both peaks increased significantly at 12mo, with 2nd peak shifting more than 1st peak (1.4ms for 1st peak and 2.4ms for 2nd peak, paired *t*-test *P*<0.001 for both peaks).

While shift of 1st first peak between 3 to 12mo in MS group was similar to LR group (*P*=0.62), the second peak demonstrated significantly larger increase of latency (3.2±3ms, *P*=0.016). Furthermore, in MS group both peaks were significantly delayed, compared to controls and LR group (*P*<0.02 for both peaks) even at 3mo after ON, which increased further at 12mo (*P*≤0.01). Correlation between latency delay of ON eyes and latency change of both peaks of fellow eyes were poor (Figure 2).

The Waveform Width of Fellow Eyes There was no significant difference between the waveform width of fellow eyes of ON and controls at 3mo or at 12mo (Table 2). Group analysis, however, revealed that, while waveform width in LR group continued to be comparable to controls, MS group showed significant increase in waveform width, which was mainly due to larger shift of the 2nd peak.

The findings of this study confirmed earlier reports by demonstrating a significantly longer latency in the fellow eyes of ON patients as compared to normal controls[6-8,12]. We have previously demonstrated a progressive deterioration in latency and amplitude of fellow eyes in patients with high risk of developing MS and in MS diagnosed patients, but not in patients with LR of developing MS[13].

Table 2 Waveform width of mfVEP at 3 and 12mo in fellow eyes

Controls (44.9±8)	*P* compared to controls
Waveform width at 3mo	
LR (44.4±9)	0.8
MS (47±7)	0.2
Waveform width at 12mo	
LR (44.8±9)	0.9
MS (49±10)	0.02

Moreover, we recently demonstrated that latency delay is related to optic radiation lesions in MS patients, who never experienced ON[6]. We also showed that there was a significant correlation between latency delay and optic radiation diffusivity indices, and temporal retinal nerve fiber layer (tRNFL) thickness which provide another evidence linking latency delay with retro-chiasmal inflammatory demyelination[6,14]. Raz *et al*[9] suggested that delayed latency in the fellow eyes of ON patients may reflect adaptive mechanisms at the cortical level. The authors hypothesized that the temporal reorganization of cortical processing, which is manifested as latency delay of the fellow eye may compensate for the delayed transmission of visual information to the cortex from the ON eye. The basis of their theory came from a cross sectional study of ON patients which showed that pattern-reversal VEP (PVEP) of fellow eyes have a wider waveform morphology, rather than delay in time-to-start response with a negligible effect from retro-chiasmal lesions.

However, PVEP can be impaired by waveform cancelation/distortion. In addition the macular over-representation, due

to large field stimulation means the effect of small peripheral visual pathway defects could be easily missed. Finally, MS lesions in the optic radiation area are often orientated to venules rather than to optic radiation fibers. This decreases the proportion of fibers damaged by a lesion and further reduces the likelihood of PVEP detection.

We hypothesized that cortical adaptive mechanisms are similar in MS and isolated ON patients and will similarly affect the latency of the fellow eye in both groups. In addition, the magnitude of the adaptive effect and, therefore, the magnitude of fellow eye latency delay should be proportional to the latency disparity between ON and fellow eyes.

Our results, demonstrate considerable differences in latency values and in the magnitude of its alteration in the fellow eye of MS compared to LR subgroups during the follow-up period. While the fellow eyes showed significant delays in comparison to controls early after ON attack, which increased even more by 12mo, this change was driven by the MS group. Thus, latency delay in fellow eyes of LR group at both 3mo and follow-up visit was statistically not different to controls for both peaks. There was however, a significant delay of first and second peaks in MS patients in comparison to both controls and LR patients.

Therefore, our data suggest that preexisting demyelinating activity may be responsible to a significant degree for the mfVEP latency delay in the fellow eye of the ON patients. This is also supported by the fact that the magnitude of the latency changes in the fellow eye observed during follow-up period did not correlate with the severity of latency delay in the affected eye.

In addition, while in LR group a similar increase of both latency peaks between 3 and 12mo was observed, MS patients demonstrated significantly larger prolongation of the second peak during follow-up period, resulting in waveform widening. The mfVEPs are largely but not entirely generated from striate cortex with some extrastriate contribution. Since this widening of the waveform was only seen in MS group, it may indicate evolving character of demyelination in primary visual cortex itself or in higher visual centers, which is related to the nature of the disseminated disease, rather than cortical plasticity.

In conclusion, while there was slight mfVEP latency change between 3 and 12mo in fellow eyes of ON patients with LR of MS that might support the hypothesis of cortical adaptation as the mechanism of its delay, the mfVEP latencies remained within normal range. The significant mfVEP latency delay in fellow eyes of MS patients and the change over time compared to the LR patients and controls supports the assumption that the changes are due to subclinical demyelination in the visual pathway outside of the affected optic nerve and reflective of the burden of disease in MS patients rather than adaptation.

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