Interrelationship of Optical Coherence Tomography and Multifocal Visual-Evoked Potentials after Optic Neuritis

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PURPOSE. Acute optic neuritis (ON) is often followed by recovery of visual function. Although this recovery is mainly attributable to resolution of the acute inflammation, the redistribution of ion channels along the demyelinated membrane, and subsequent remyelination, part of it may be the result of neural plasticity. In the present study, the interrelationship was examined between structural (retinal nerve fiber layer [RNFL] thickness) and functional (amplitude of multifocal visual evoked potentials [mfVEPs]) measures of the integrity of the visual pathway in the postacute stage of ON, to determine whether there was any evidence of ongoing neural reorganization.

METHODS. Twenty-five subjects with acute unilateral ON underwent serial RNFL thickness measurement and mfVEP recording. The inter-eye asymmetry of both measures was analyzed. In the period between 6 and 12 months, the subjects were considered free of optic disc edema, and that period was used to analyze the structure–function relationship. Twenty control subjects were also examined.

RESULTS. There were significant but opposite changes in RNFL thickness and mfVEP amplitude. The average asymmetry of RNFL thickness between affected and fellow eyes increased from 17.5 ± 11.5 to 21.1 ± 12.8 μm (P = 0.0005), indicating progressive axonal loss, whereas mfVEP amplitude asymmetry decreased from 46.6 ± 32.4 to 38.3 ± 31.1 nV (P = 0.0015), indicating continuous functional recovery. In comparison to the 6-month results, the mfVEP amplitude in the ON eye improved by 17.8%, whereas RNFL thickness decreased by 20.8%. The result remained unchanged regardless of the degree of optic nerve remyelination.

CONCLUSIONS. The finding of structural–functional discrepancy at the postinflammatory stage may support the concept that neural plasticity contributes to functional recovery after acute ON. (Invest Ophthalmol Vis Sci. 2010;51:2770–2777) DOI: 10.1167/iovs.09-4577

A cute optic neuritis (ON) is often followed by recovery of visual function, even if accompanied by significant optic nerve atrophy.2–4 The recovery has been attributed to resolution of acute inflammation, redistribution of ion channels along the demyelinated membrane, and subsequent remyelination.5–8 It has also been suggested that part of the recovery is the result of neural plasticity.

Retinal nerve fiber layer (RNFL) thickness as measured by optical coherence tomography (OCT) has recently been suggested to be an indicator of axonal loss in the optic nerve.4–5,10 During an acute inflammatory attack, spillover edema often results in thicker RNFL measurements,11 which diminish with resolution of the inflammation. Subsequent retrograde axonal degeneration causes thinning of the RNFL,12–15 even in patients with good visual recovery,16 and it has been found to correlate with other structural measures of axonal integrity.17 Visual evoked potentials (VEPs) are an objective means of measuring the function of the visual pathway and are understood to be generated at the level of the striate cortex by combined activity of postsynaptic potentials.18,19 The magnitude of the VEP reflects the number of functional afferent fibers reaching the striate cortex and the degree of synaptic activity in V1. In ON, the number of functional afferent fibers is determined by a combination of two factors: the severity of the inflammation and axonal degeneration along the visual pathway.14,20 Therefore, diminished VEP amplitude indicates inflammatory conduction block, axonal atrophy, or a combination of both. The increase in amplitude, on the other hand, is a consequence of resumed conduction in previously blocked fibers due to resolution of inflammation and edema or possibly expansion of synaptic activity along the visual pathway up to the level of V1. Delayed conduction of VEP has also been found in a high proportion of patients with ON and is thought to reflect demyelination of the optic nerve fibers,21,22 with the subsequent shortening of latency thought to represent the process of remyelination.20,25

Conventional full-field VEP is greatly dominated by the macular response due to its cortical overrepresentation.23 In contrast, mfVEP enables simultaneous recording from multiple regions of the visual field, allowing assessment of a much larger cross-sectional area of the optic nerve and therefore more accurate functional evaluation of the visual pathway.25,26

High topographic correlation between RNFL thickness and mfVEP amplitude has recently been demonstrated by our group in a cross-sectional study of late postacute ON.14,27 However, at the early stage after ON, both RNFL thickness and mfVEP amplitude are influenced by two independent processes—acute inflammation and axonal loss—and the effect of
those processes on structural and functional measures is quite different. Although inflammation reduces mfVEP amplitude due to conduction block, in some cases, it increases RNFL thickness as a result of vasogenic edema.\textsuperscript{5–7,28,29} Axonal loss, on the other hand, leads to parallel changes in both measures, causing thinning of the RNFL and reduction of the mfVEP amplitude.

In the present study, we examined the association between longitudinal changes in RNFL thickness and amplitude of mfVEP within the first 12 months after the onset of ON, to gain better understanding of the relationship between structural and functional mechanisms during the process of recovery from ON.

**METHODS**

**Subjects**

Twenty-five subjects with clinically diagnosed acute unilateral ON (unilateral visual loss, afferent papillary defect, pain on eye movement) and no previous demyelinating events were enrolled. All patients had at least one brain or spinal cord demyelinating lesion detected on initial (within 1 week of onset) examination by magnetic resonance imaging (MRI), but did not fulfill the Barkhof and Tintore criteria for dissemination in space, as described in the recommendations of an international panel on the diagnosis of multiple sclerosis (MS).\textsuperscript{30} and were classified as high risk for development of MS. Exclusion criteria were atypical presentation, bilateral ON, recurrent ON, and a history of any other ocular disease. All patients had completed a 3-day course of 1 g per day intravenous methylprednisolone and a 2-week oral taper of steroids.

mfVEP recording and OCT testing were performed at 1, 3, 6, and 12 months from onset of ON. Twenty age- and gender-matched control subjects were also examined by mfVEP and OCT. The eligibility criteria for control subjects included 6/6 vision in both eyes and normal results on ophthalmic examination. OCT and VEP were performed twice with an interval of 1.5 to 2 months.

Procedures adhered to the tenets of the Declaration of Helsinki, and informed consent was obtained from all participants.

Statistical analysis was performed with commercial software (Statistica 4.1; StatSoft, Tulsa, OK).

**mfVEP Recording and Analysis**

Multifocal mfVEP testing was performed with a commercial system (Accumap; ObjectiVision Pty. Ltd., Sydney, Australia) employing standard stimulus conditions described in detail elsewhere.\textsuperscript{31} Briefly, the stimulus consisted of a cortically scaled cardboard pattern of 58 segments (eccentricity up to 24°) (Fig. 1A). Each segment contained a 4 × 4 grid of black (1.1 cd/m\textsuperscript{2})-and-white (146 cd/m\textsuperscript{2}) checks (Michelson contrast, 99%), which reversed patterns according to a binary pseudorandom sequence. The visual stimulus was generated on a 21-in. display. All recordings were performed monocularly. Four gold-cup electrodes (Grass Telefactor, West Warwick, RI) were used for bipolar recording, with two electrodes placed 4 cm on either side of the inion and one electrode 2.5 cm above and one 4.5 cm below the inion in the midline. Electrical signals were recorded along four channels, showing the difference between readings at the superior and inferior electrodes, the left and right electrodes, and, obliquely, the horizontal and inferior electrodes. Visual evoked responses were amplified 1 × 10\textsuperscript{5} times and band-pass filtered 1 to 20 Hz.

Opera software (Accumap; ObjectiVision Pty. Ltd., Sydney, Australia) correlated the pattern-reversal binary sequence with the electrical signals recorded and a response for each segment was obtained. The largest peak-trough amplitude within the interval of 70 to 210 ms was determined for each channel. For amplitude analysis, the wave of maximum amplitude among the four channels was automatically selected by the software, to create a combined topographic map (Fig. 1B).\textsuperscript{32} For latency analysis, traces from the same channel were selected for all four tests for each segment of the visual field by a custom-designed algorithm.\textsuperscript{25} Averaged values of both amplitude and latency, which were used in the final analysis, were calculated by averaging the amplitude and latency of the individual sectors.

**OCT Recording and Analysis**

OCT was performed (Stratus OCT-3 scanner; version 3.0, Carl Zeiss Meditec Inc., Dublin, CA), with the Fast RNFL protocol, consisting of three circular scans with diameters of 3.4 mm centered on the optic disc. The pupils were not dilated. The OCT scan was considered acceptable if the signal strength score was 7 or more. The mean total RNFL thickness was assessed.

**Asymmetry Analysis**

Intersubject variability in both OCT and mfVEP is high\textsuperscript{33,34} and may mask the relationship between the two measures.\textsuperscript{17} To minimize its effect, the inter-eye asymmetry of RNFL thickness and amplitude and the latency of the mfVEP was calculated as a difference between fellow and ON eyes and was expressed in micrometers, nanovolts, and milliseconds, respectively.\textsuperscript{17,54}

Latency recovery was the percentage of latency asymmetry reduction at 12 months compared with latency asymmetry at 1 month.\textsuperscript{14}

Our previous study demonstrated high topographic correlation between the thickness of RNFL sectors and mfVEP amplitude of corresponding areas of the visual field,\textsuperscript{27} which was, however, weaker than averaged data. The greater variability of smaller regions compared with the global data was cited as a possible reason for the better global than sectoral correlations. In the present study we were looking at longitudinal changes in the two parameters (i.e., the trends of these values over time). The global parameters are once again likely to be more robust than the sectoral ones, particularly considering the small magnitude of the changes. Therefore, global (averaged) parameters (both RNFL thickness and mfVEP amplitude) were used for the analyses. Equal weight was given to all sectors (58 sectors for mfVEP and 4 sectors for OCT) to obtain averaged values.

**RESULTS**

Demographic data are presented in Table 1.

By the end of the follow-up period, 5 patients converted to clinically definite MS, and 20 remained at high risk. However only three of the five converts initiated disease-modifying therapy (Avonex; Biogen Idec, Cambridge, MA). Therefore, we believe that the effect of treatment on the result of this study is minimal, if any.

Averaged RNFL thickness and mfVEP amplitude data from the ON and fellow eyes are presented in Figure 2. There was a significant change in both parameters in the ON eye during the follow-up period (\(P < 0.0001\), one-way ANOVA), resulting in the progressive reduction of RNFL thickness and increase of the mfVEP amplitude. In the fellow eye, both parameters remained unchanged (\(P = 0.89\) and \(P = 0.4\) respectively, one-way ANOVA). The difference between two consecutive test results for RNFL thickness and mfVEP amplitude in the fellow eye was considerably less than the test–retest variability in the control subjects (average test–retest variability of RNFL thickness for controls was 2.9 \(\mu\text{m}\), and average test–retest variability of mfVEP amplitude was 7.4 \(\text{mV}\)). Therefore, stable values of both parameters in the fellow eyes justified the use of inter-eye asymmetry.

**Changes in RNFL Thickness Asymmetry**

There was a wide range of RNFL asymmetry at initial (1 month) testing, from highly negative (RNFL of the affected eye thicker than in the fellow eye) to highly positive (RNFL of the affected eye thinner than in the fellow eye), resulting in almost no RNFL thickness asymmetry, on average (–1.2 ± 11.6 \(\mu\text{m}\); range, –10.3 to 20.6).

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Over subsequent visits, RNFL thickness demonstrated a consistent trend of increasing inter-eye asymmetry ($P < 0.0001$, repeated-measures ANOVA), with the affected eyes showing progressively thinner RNFLs (Fig. 3A).

Changes in mfVEP Amplitude Asymmetry

While amplitude asymmetry at baseline varied significantly among the patients, it was, on average, very high ($84.6 \pm 45.3$ nV) and always positive (range, 13–183 nV), indicating considerable reduction of amplitude in the affected eye (Fig. 3B). There was a clearly observable trend of amplitude asymmetry changes over time. However, contrary to the evolution of RNFL thickness, changes in mfVEP amplitude inter-eye asymmetry progressed in the opposite direction, demonstrating gradual reduction (i.e., amplitude recovery) over time ($P < 0.0001$, repeated-measures ANOVA).

Correlation between RNFL Thickness and mfVEP Amplitude

As described in the introduction, true examination of the structure–function relationship is only possible after swelling of the optic nerve subsides. We hypothesized that the gradual reduction of the edematous component would lead to an increase in correlation between RNFL thickness and mfVEP amplitude as the effect of axonal loss became more dominant. The time point when the correlation reaches maximum and stabilizes would therefore mark the full resolution of edema. The correlation between RNFL thickness and mfVEP amplitude was determined, to establish this time point.

There was a nonsignificant negative correlation between the inter-eye asymmetry of RNFL thickness and that of mfVEP amplitude at 1 month (Fig. 4A, $r^2 = 0.01$, $P = 0.42$), consistent with vasogenic edema in the acute phase, causing an increase.

**Figure 1.** (A) Multifocal cortically scaled stimulus used in mfVEP recording. Each sector (area $4 \times 4$ checks) reversed polarity according to an individual pseudorandom sequence. (B) Example of mfVEP recorded from a patient with ON. Expanded traces from one of the segments demonstrated lower amplitude and delayed latency in the ON eye (bottom) compared with that in the fellow eye (top).
in RNFL thickness, but a reduction in mfVEP amplitude. Over the next two visits, the correlation became progressively more positive and stronger, suggesting the diminishing role of optic nerve edema in measured RNFL thickness and unmasking the association between RNFL atrophy and low mfVEP amplitude (Figs. 4B, 4C). The correlation reached a maximum of $r^2 = 0.53$ ($P = 0.0001$) at 6 months, remaining at a similar level after a further 6 months ($r^2 = 0.51$, $P = 0.0001$; Fig. 4D). This value was similar to that reported during the late post-ON stage. Stabilization of this relationship at 6 months supports complete resolution of edema. Therefore, changes in RNFL thickness and mfVEP amplitude between 6 and 12 months were closely analyzed to examine the true relationship between structure and function.

**Structure–Function Discrepancy at the Post-acute Stage**

Analyses of RNFL thickness and mfVEP amplitude between 6 and 12 months revealed that changes of both measures during this period were significant and, while similar in magnitude, progressed in opposite directions. The average asymmetry of RNFL thickness increased from $17.5 \pm 11.5$ to $21.1 \pm 12.8 \mu m$ ($P = 0.0003$, Student’s paired $t$-test) indicating progressive thinning of the RNFL in the ON eyes. Contrary to that, mfVEP amplitude asymmetry decreased from $46.6 \pm 32.4$ to $38.3 \pm 31.1$ nV ($P = 0.0015$, Student’s paired $t$-test) during the same period, implying continuous recovery of amplitude in ON eyes. In comparison to the 6 month results, mfVEP amplitude asymmetry fell (amplitude improved) by 17.8%, whereas RNFL thickness asymmetry increased (RNFL thickness worsened) by 20.8%. The scatterplot presented in Figure 5 shows how individual levels of RNFL thickness (Fig. 5A) and mfVEP amplitude (Fig. 5B) changed between 6 and 12 months in the ON patients compared with changes between the results of the two test in the control subjects.

**Table 1.** Demographic Data of ON Patients and Normal Control Subjects

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<th>ON Patients</th>
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<tr>
<td>Subjects, $n$</td>
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<td>20</td>
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<tr>
<td>Male:female ratio</td>
<td>1:2.5 (7/18)</td>
<td>1:2.5 (6/14)</td>
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<tr>
<td>Mean age ± SD</td>
<td>32.6 ± 9.9</td>
<td>35.9 ± 11.2</td>
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<tr>
<td>$P$</td>
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Visual acuity at onset

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<td>≥6/9, ≥6/30</td>
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Visual acuity at 12 months

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<td>≥6/9, ≥6/30</td>
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<tr>
<td>&lt;6/30</td>
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Age between the two groups was not significantly different ($P = 0.12$).

**Figure 2.** Averaged (A) RNFL thickness and (B) mfVEP amplitude in ON and fellow eyes during the follow-up period. Bars, SD.

**Figure 3.** Change in inter-eye asymmetry of (A) RNFL thickness and (B) mfVEP amplitude during the follow-up period. Bars, SD.
Structure–Function Discrepancy and Remyelination

The effect of myelin loss and recovery in optic nerve lesions can be qualitatively measured by the latency delay of the VEP,\(^2\),\(^21\),\(^36\) which reflects the reduction of conduction speed along neural fibers due to change from saltatory to continuous conduction\(^37\) or increase in conduction speed, with the reversal of this process during remyelination.\(^38\) Therefore, to investigate the possible effect of remyelination on the discrepancy in structure–function, the patients were subdivided into two groups based on longitudinal changes in latency asymmetry and the test–retest variability, reported previously.\(^23\) Group 1 comprised patients who exhibited significant (exceeding test–retest variability) improvement in latency asymmetry during the follow-up period (latency recovery or remyelinating group), whereas group 2 included patients with poor (less than test–retest variability) or no recovery of latency asymmetry (latency nonrecovery or nonremyelinating group). Amplitude and RNFL changes were examined and compared between the groups to look for the possible effect of latency recovery on axonal loss and amplitude increase. There were 13 patients in group 1 and 9 in group 2. Amplitude in three cases was too low to determine latency at onset.

Figures 6A and 6B demonstrate changes in mVEP amplitude and RNFL thickness in both groups between 6 and 12 months.

**mVEP Amplitude in the Latency Groups.** Two observations become apparent with respect to the amplitude. First, both groups demonstrated a similar tendency toward amplitude recovery (Fig. 6A). In both groups, changes between 6 and 12 months were statistically significant (amplitude asymmetry fell by 20.3% and 19.5%, \(P = 0.02\) and 0.039 for the remyelinating and nonremyelinating groups respectively, paired Student’s \(t\)-test). Second, the magnitude of amplitude asymmetry was greater in the nonremyelinating group at both time points (\(P = 0.047\) and 0.062 for 6 and 12 months respectively, Student’s \(t\)-test).

**RNFL Thickness in the Latency Groups.** Changes in RNFL thickness in the latency groups between 6 and 12 months are shown in Figure 6B. Both groups displayed similar tendencies of increasing RNFL asymmetry with time. Statistically significant increases were observed in both groups be-
The data are sparse on the long-term evolution of RNFL thickness after an episode of ON. A recent serial study demonstrated no significant RNFL thinning after 6 months from the onset of ON. However, different patient selection criteria may be responsible for this disagreement. Thus, although only patients with MRI changes typical of demyelination were enrolled in our study, Costello et al. included all patients with ON, regardless of MRI findings. Therefore, our cohort was more likely to have ongoing subclinical inflammation, which may result in progressive RNFL thinning. A progressive loss of optic nerve fibers even 1 year after the attack was also detected in longitudinal MRI studies of the mean area of the optic nerve. Loss of optic nerve fibers limits the transmission of the afferent stimulus to the visual cortex. We expected, therefore, that in the postacute period, changes in amplitude of the mVEP would decline in parallel with changes in optic nerve structural integrity measure (RNFL thickness). In other words, we expected that progressive axonal degeneration would lead to progressive decline of the mVEP amplitude. However, contrary to our expectation and despite the loss of RNFL fibers, significant improvement in mVEP amplitude was noted in the interval between 6 and 12 months.

Several longitudinal studies of full-field VEPs in ON have demonstrated improvement in amplitude in the early postacute period, with no significant changes afterward. However, to the best of our knowledge, the discrepancy between continued RNFL thinning and the increase in mVEP amplitude beyond 6 months after ON is a new finding. A few possible explanations for the discovered trend can be suggested.

First, continuous remyelination may play an important role in long-term functional improvement. Histologic and experimental studies have demonstrated that restoration of myelin can start shortly after a demyelinating event and its extent varies from complete absence to partial or full remyelination of the lesion. Remyelination of MS lesions may have different important functions such as lesional repair, protection of axons, and restoration of conduction velocity. Recent studies have suggested that myelin plays an important role in providing trophic support to axons and protects them from inflammatory mediators and immune effector cells. Therefore, it may be argued that continuous remyelination has a positive effect on axonal conductivity and is responsible for the increase in cortical amplitude noted.

We investigated this question by separating the patients into two groups based on the degree of recovery of mVEP latency. The subanalysis performed demonstrated that even though the amplitudes were lower and the RNFL thinner in those patients who did not recover latency compared with those who did, both groups showed similar significant increases in amplitude combined with a parallel decline in RNFL thickness. This finding suggests that remyelination alone cannot explain our finding of a structural–functional discrepancy.

Second, the presence of neuronal reserve in the anterior visual pathway is well known, and functional deficits do not often manifest until a substantial number of nerve fibers have been destroyed. This process may contribute to the excellent recovery of vision and VEP amplitudes in the early postacute period, often encountered even in the presence of identifiable nerve fiber atrophy. However, continuous improvement in mVEP amplitude long after the resolution of the acute inflammation indicates that this is not a likely explanation.

Third, amplitude asymmetry may also decline, not only because of an increase in ON eye amplitude, but also due to a reduction of amplitude in the fellow eye as a result of resolution of the early compensatory enhancement or progressive subclinical inflammation. However, although there were some fluctuations of amplitude in the fellow eye, there was no
observable trend, and variations never exceeded test–retest variability. RNFL thickness of the fellow eye also remained constant during the follow-up period.

Finally, neural reorganization has been described after acute ON and is considered to be one of the mechanisms responsible for the recovery of function from the acute attack. Various mechanisms, including increased expression of sodium channels, neuronal or synaptic changes, increased recruitment of parallel pathways, and cortical reorganization, including functional expansion of surviving neurons,37,55–55 are thought to be involved in this process. These mechanisms have been studied fairly extensively with fMRI imaging. Although the most common finding of fMRI studies is a strong association between the level of inflammation and reduction in cortical activation within the visual cortex,44,56–58 some studies have also demonstrated extensive activation of the extraoccipital areas during recovery from ON, indicating significant functional reorganization of the cortex.44,56 However, apart from a single study by Toosy et al.,44 none of the fMRI investigations compared functional outcome with structural markers of optic nerve axonal injury as the factor limiting cortical input.

Our findings of increased postsynaptic activity in the striate cortex (as measured by the improvement of the mfVEP amplitude) coupled with simultaneous reduction of cortical input (RNFL thinning) may support the concept of continuous cortical reorganization in postacute ON. The magnitude of this change in absolute terms was quite small during the interval studied. However, the time interval used to study this effect was chosen to exclude the effect of vasogenic edema, which may obscure the relationship in question.

The exact site of neuroplasticity in the hierarchy of the visual system remains a matter of controversy. Thus, data by Korsholm et al.3 implicated the lateral geniculate nucleus (LGN) as a primary site of cortical adaptation, whereas others have demonstrated significant involvement of the wider extra- striate network, including the peristriate or lateral occipital complex.44,56 We are unable to precisely localize the possible adaptive changes reported in the present study. However, since the mfVEP is generated at the striate cortex59,60 changes that we recorded are most likely occurring below or at that level.

Our findings are in concordance with those of other studies of the structure–function relationship after ON. Serial analyses of eyes with ON performed by Sergott41 showed that reductions in RNFL thickness occurs despite the recovery of visual acuity. Similar relationships were evident in a serial MRI study, which described the lack of association between the optic nerve mean area and visual outcome at 1 year and suggested that it may reflect neural plasticity or remodeling of function within the visual system.41

Of some interest are incidental findings of amplitude and RNFL thickness changes with respect to remyelination. Thus, the smaller mfVEP amplitudes and thinner RNFLs (after 6 months) in the group of patients who did not recovered latency compared with those who did points out a possible association between the level of axonal loss and the degree of remyelination.

This study was limited by the small sample size and relatively short follow-up, especially in the context of MS. Further follow-up of these patients using the same modalities will improve our understanding of the various processes involved in axonal injury and repair in MS.

References

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