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Motion-onset visual evoked potentials improve the diagnosis of glaucoma

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Abstract. Chronic glaucoma has been shown preferentially to damage larger retinal cells and optic nerve fibres that provide the input to the magnocellular visual pathway. We compared the motion-onset visual evoked potentials (primarily the magnocellular system) with those to standard pattern reversal in 20 patients with bilateral chronic glaucoma. For motion-onset visual evoked potentials, the pattern (isolated 40′ checks of 10% contrast) moved in four cardinal directions (varied randomly from trial to trial) at a velocity of 10 deg/s for 20 ms, with an interstimulus interval of 1 s. In pattern-reversal stimulation, the checkerboard reversed at a rate of 2 reversals per second. In 60% of the eyes investigated, the results of both types of visual evoked potentials correlated, showing either normal (27.5%) or increased (32.5%) latencies. In the remaining 40% of the eyes, the normal pattern-reversal visual evoked potential latencies were accompanied by prolonged motion-onset visual evoked potentials. The high occurrence of delayed motion-onset visual evoked potentials in our patients confirms the primary magnocellular loss in chronic glaucoma and suggests that the motion-onset VEPs are suitable for detection of glaucomatous changes.

Introduction

The diagnosis of chronic simple glaucoma is straightforward when elevated intraocular pressure is accompanied by characteristic optic nerve head cupping and visual field defects. However, especially in early stages of glaucoma, some of these three basic glaucomatous signs, especially the typical visual field defects, can be missing. In these cases, electrophysiologic methods—visual evoked potentials (VEPs) and electroretinogram (ERG)—can be helpful because they are able to detect subtle damage to retinal ganglion cells and their fibers before the damage can be found by traditional static perimetry.

In histologic studies of glaucomatous optic nerve damage in humans and monkeys, Quigley and co-workers [1, 2] observed a selectively greater loss of large optic nerve fibers that provide the principal retinal input to the magnocellular pathway, which is considered to be primarily involved in motion,

flicker and depth discrimination [3]. A number of psychophysical studies [4–7] have provided support for the hypothesis of selective magnocellular damage in glaucoma, for example, elevated motion detection threshold [5] or impaired minimum and maximum displacement thresholds [7] in glaucomatous patients. These findings prompted us to examine motion-onset VEPs in glaucomatous patients. The motion-onset VEPs seem to be specific for magnocellular pathway testing [8] and display lower interindividual variability and higher signal-to-noise ratio of the motion-specific component in comparison with other motion-related VEPs (motion-offset, motion-reversal) [9, 10].

We compared results of the motion-onset VEPs with transient pattern-reversal VEPs the main component of which—P100—probably reflects the function of the parvocellular form and color detecting pathway [8].

Materials and methods

Subjects. The monocular VEPs were tested in a group of 20 patients with variously advanced bilateral glaucoma; their clinical details are given in Table 1. Visual acuity shown in Table 1 was measured at 4 m by means of conventional Landolt C charts [11]. Glaucoma had been diagnosed in referring eye departments before the patients were examined in our laboratory. All patients (except two with low-tension glaucoma) had increased intraocular pressure (measured by Goldmann applanation tonometer), which in some eyes was already being treated at the time of our examination. Optic disc cupping (cup-disc ratio, ≥ 0.3) and typical visual field defects (assessed by Humphrey computer-assisted perimeter) were present in all patients. Almost all patients were taking nonmiotic medication (betaxolol hydrochloride or timolol maleate); in two who were taking pilocarpine the latency of VEPs was corrected post hoc for miosis according to Towle et al. [12].

Recording and analysis. All recordings were performed in a sound-attenuated, electromagnetically shielded chamber with a background luminance of 1 cd/m^2. The subject was seated in a comfortable dental chair with a neck support to reduce muscle artifacts. A dark fixation point of 15′ diameter was placed in the center of the stimulus field, and the subjects were instructed not to follow the moving or reversing pattern with their eyes.

The stimuli were generated on a computer monitor (ViewSonic 21; 100 frames per second; total display size, 30° × 40°) under computer control (PC 486).

Table 1. Clinical details of patients with glaucoma

Subject	Age (y)	Sex	Eye	Visual Acuity	C/D	IOP	Therapy	PREP (ms) P100 latency	MVEP (ms) N160 latency
1	19	F	LE	4/10	0.8	20	Betaxolol	118	150
			RE	4/12	0.8	22		110	150
2	53	F	LE	4/4	0.3	20	Betaxolol	104	150
			RE	4/4	0.3	25		98	152
3	16	F	LE	4/8	0.7	15	Betaxolol	90	168
			RE	4/8	0.7	15		94	170
4	66	F	LE	4/6	0.3	20	Betaxolol	98	184
			RE	4/4	0.4	22		96	184
5	45	M	LE	4/12	0.5	20	None	96	202
			RE	4/8	0.5	20		102	202
6	40	M	LE	4/4	0.3	21	Timolol	106	184
			RE	4/4	0.3	21		98	180
7	26	M	LE	4/10	0.4	24	Betaxolol	98	156
			RE	4/10	0.4	26		110	186
8	26	F	LE	4/4	0.4	24	Betaxolol	110	188
			RE	4/4	0.4	26		106	186
9	14	F	LE	4/10	0.8	24	Timolol	104	206
			RE	4/6	0.8	21		102	198
10	44	F	LE	4/6	0.7	23	Timolol	108	194
			RE	4/6	0.7	23		108	196
11	51	M	LE	4/12	0.8	19	Timolol	122	204
			RE	4/8	0.7	19		120	210
12	70	M	LE	4/12	0.8	16	Betaxolol	112	220
			RE	4/8	0.6	16		116	196
13	40	F	LE	4/8	1.0	21	Timolol	114	186
			RE	4/8	1.0	16		122	188
14	55	F	LE	4/10	0.4	20	Betaxolol	120	194
			RE	4/6	0.8	25		132	220
15	46	M	LE	4/10	6.0	23	Timolol	136	222
			RE	4/10	0.5	23		140	200
16	46	M	LE	4/6	1.0	14	Betaxolol	128	204
			RE	4/8	1.0	15		152	208
17	53	M	LE	4/4	0.8	25	Betaxolol	130	190
			RE	4/4	0.8	25		136	192
18	65	F	LE	4/10	1.0	25	Timolol	134	210
			RE	4/10	1.0	30		140	244
19	62	M	LE	4/8	0.4	25	Timolol	132	192
			RE	4/8	0.4	26	+pilocarpine	128	200
20	60	F	LE	4/12	1.0	20	Pilocarpine	150	220
			RE	4/10	1.0	20		142	210

For motion-onset VEPs, the stimuli consisted of isolated 40′ checks (with 2° distance between each other) of 10% contrast and mean luminance of 17 cd/m^2. This pattern moved in one of four cardinal directions (up, down, left or right, changed randomly from trial to trial) at a velocity of 10 deg/s for 200 ms and was presented stationary during a 1-s-long interstimulus interval.

For pattern-reversal VEPs, the high-contrast (98%) checkerboard of 40′ element size alternated at the rate of 2 reversals per second.

Monocular VEPs were recorded in the bipolar lead O_Z-C_Z and in three unipolar leads with the electrodes placed at O_Z and 5 cm to the right and to the left from this point—O_R and O_L. The lateral electrodes are more convenient for motion-onset VEP recordings, since the maximum of this type of VEP is usually located over the right or left occipital area [9, 13]. Linked earlobes served as reference. After amplification (Tektronix AM 502) in the 0.1–100-Hz band, 100 epochs of 400-ms duration were averaged on a personal computer with a sampling rate of 500 Hz.

In the recordings, only the latencies of the dominant VEP peaks were evaluated—in the pattern-reversal VEPs those of the main P100 peak and in the motion-onset VEPs those of the N160 peak. The upper and lower limits of normal were 125 ms in the pattern-reversal VEP and 184 ms in the motion-onset VEP. These values represent the mean + 2.5 SD obtained by examination of 50 healthy subjects with about the same mean age (42.3 ± 12 years) as the glaucoma group (44.8 ± 17 years). The parameters given in further text are always from the channel with the largest amplitudes (from O_Z–A_{1+2} in the pattern-reversal VEPs and from either O_L–A_{1+2} or O_R–A_{1+2} in the motion-onset VEPs).

Results

In Figure 1 the values of pattern-reversal and motion-onset VEP latencies for all examined eyes (n = 40) are plotted pairwise. All the eyes that exhibited prolonged pattern-reversal VEP latencies (32.5%) also had prolonged motion-onset VEP latencies. However, 40% of glaucomatous eyes displayed the abnormal motion-onset VEP latencies accompanied by completely normal pattern-reversal VEP latencies.

The scatter diagrams in Figure 2 plot the latencies of the pattern-reversal and motion-onset VEPs as a function of the extent of optic nerve head cupping (upper diagrams) and of the degree of perimetric deficit (lower diagrams). The open circles represent the eyes that exhibited normal latencies of VEPs; the solid circles show those eyes in which the abnormal latencies were found. The latency of the pattern-reversal as well as of the motion-onset. VEPs is significantly ($p < 0.001$) increased with both increasing cup-disc ratio

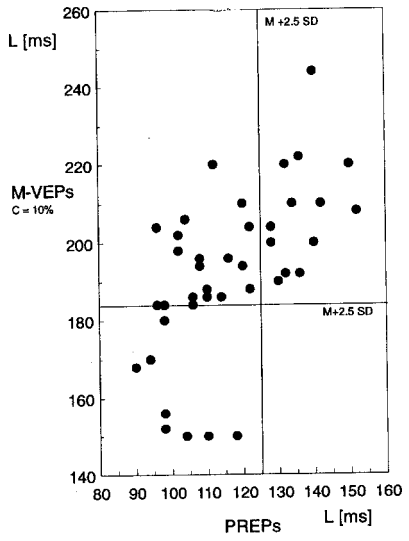

Figure 1. Distribution of pattern-reversal VEP (PREP) versus motion-onset VEP latencies (M-VEPs) of the 40 eyes of all the patients with glaucoma. Upper limits of both latencies (mean + 2.5 SD of the normal values in the control group) are shown.

(correlation coefficients, 0.55 and 0.44) and the severity of perimetric changes (correlation coefficients, 0.74 and 0.62). However, there was a considerable difference in dependence of both types of VEPs on the perimetric findings. While the prolonged latencies of the pattern-reversal VEPs could be found only in the late perimetric changes (stages 5, 6 and 7; see legend to the figure) involving at least to some extent the central retina, the increased motion VEP latencies occurred even for the earliest defects.

This fact is also shown in the two concrete examples depicted in Figures 3 and 4. Figure 3 shows that the visual field defects were restricted to the retinal periphery only, and this was the reason why the pattern-reversal VEPs were within the normal limits in both eyes. In contrast, the motion-onset VEP latencies were increased for the full-field stimulation and could not be identified for peripheral stimulation alone, produced by covering the central 20° diameter of the screen by mask. Since in the case shown in Figure 4 the very advanced glaucomatous visual field defects were present, the abnormal motion-onset VEPs were also accompanied by abnormal pattern-reversal VEPs.

Because some of the patients displayed lower visual acuity (Table 1), we were also interested whether the visual acuity itself could account for the VEP latency increase. We did not find any significant correlation between individual visual acuities and both pattern-reversal and motion-onset VEP

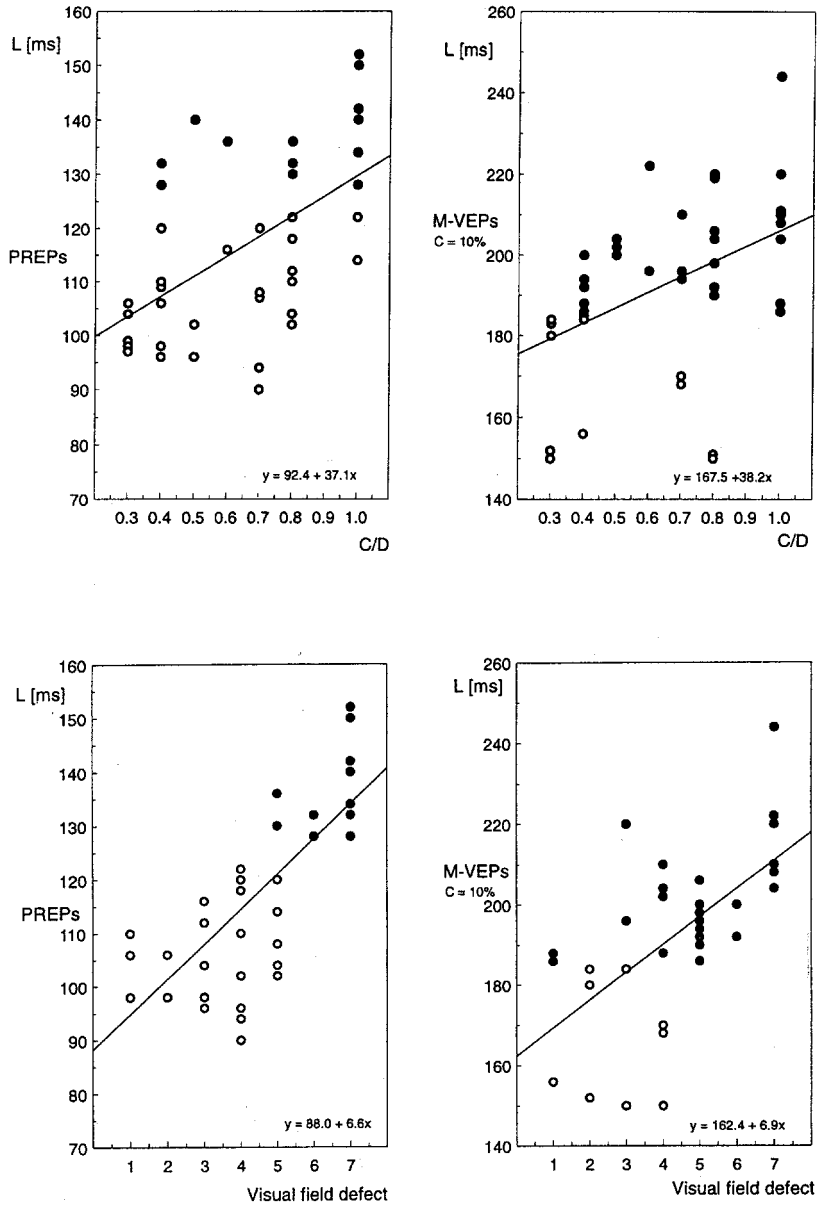

Figure 2. Latency of pattern-reversal VEP (PRBP) and motion-onset VEP (M-VEP) as a function of cup-disc ratio (C/D) and degree of visual field defects (1, generalized reduced sensitivity; 2, isolated paracentral scotomata; 3, paracentral scotomata and nasal step or temporal wedge; 4, concentric field reduction up to central 20°; 5, concentric reduction up to 10° or peripheral breakthrough; 6, concentric reduction up to central 5°; 7, defects involving the central 5° of the visual field). Open circles represent the eyes with normal VEP latencies; solid circles show those in which the VEP latencies were abnormally delayed. Regression lines and coefficients are shown.

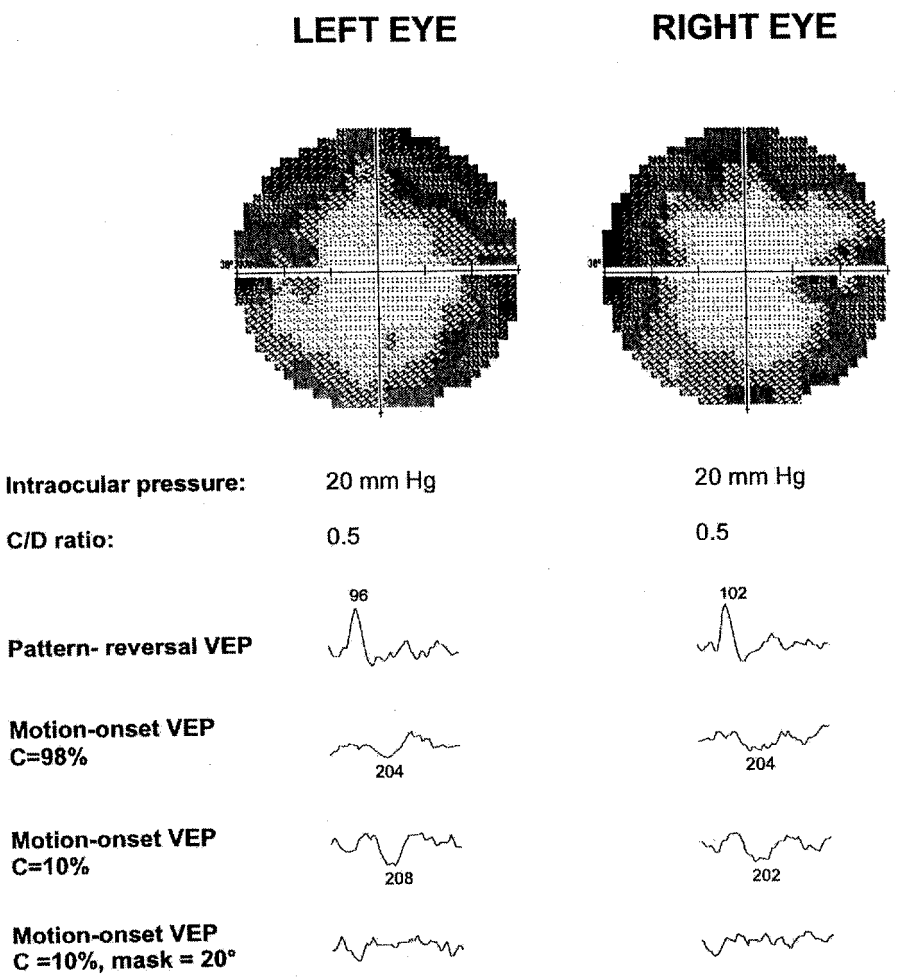

Figure 3. Example of pattern-reversal and motion-onset VEP findings from a patient with peripheral visual field loss (outside the central 20°–25°). Values of the intraocular pressure and cup-disc (C/D) ratio at the time of VEPs testing are added. While the motion-onset VEPs show clear abnormality (delayed latency to full-field stimulation and no distinguishable response to stimulus restricted to the peripheral visual field), the pattern-reversal VEPs are fully normal.

latencies. This finding is not surprising because 40′ checks were sufficiently large for the visual acuity values of our patients.

Discussion

Glaucoma has been reported to affect pattern-reversal VEPs, causing a phase shift in the steady-state VEPs and/or a reduction in amplitude and an increase

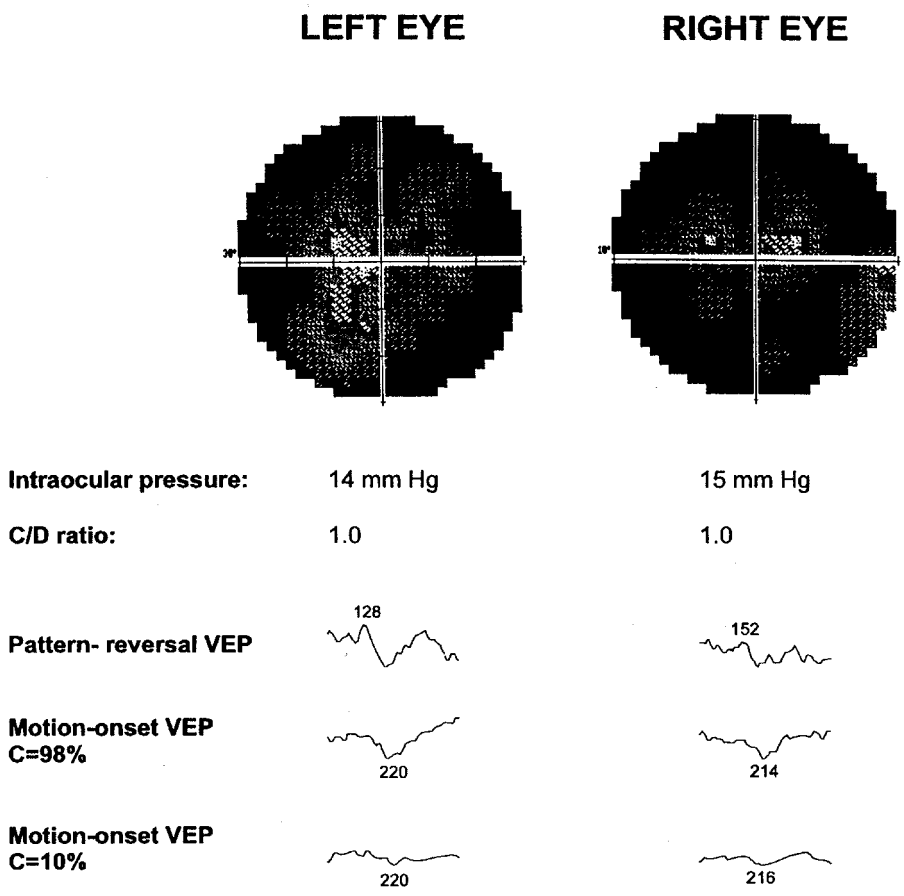

Figure 4. Example of pattern-reversal and motion-onset VEP findings from a patient with very advanced glaucoma. Visual field defect involves even the central retina (note that only central 10° perimeter is given for the right eye), and consequently, not only the motion-onset but also the pattern-reversal VEPs have prolonged latencies.

in latency of the main P100 peak in the transient VEPs [12, 14–17]. Although it has been suggested that transient and steady-state reversal VEPs are complementary methods for visual system testing [18], according to Tobimatsu et al. [19] the phase alterations of the steady-state VEPs provide approximately the same information as P100 latency delay of the transient VEP. Whether the steady-state pattern-reversal stimulation activates only the parvocellular or also the magnocellular pathway is not clear so far [20]. However, for the transient reversal VEP, we have shown [8] that the main P100 peak is probably of parvocellular pathway origin, while the following negative peak (not constant and distinct in all subjects) might result from the magnocellular

pathway activity. That is why the P100 latency abnormalities seem to be reliable indicators of glaucomatous damage to the parvocellular neurons. In our patients we have found P100 latency changes in only 32.5%, which is less than in other studies on this topic; for example, Howe and Mitchell [16] found absolute P100 latency delays in 44.4% of glaucomatous eyes and Bray et al. [21] 41.8%. This difference might be caused by different frequencies of more advanced glaucoma in tested groups of patients or by the fact that in both mentioned studies larger checks (100′) were used for pattern-reversal stimulation, which might enable the testing of more peripheral parts of the retina.

Similar to Towle et al. [12], we found a positive correlation between the increasing pattern-reversal VEP latencies and extent of optic disc cupping as well as between the pattern-reversal VEP findings and the progress of visual field defects. In our patients the delayed P100 latencies occurred only in patients with more severe field defects that at least partially involved the central 15° of the retina, that is, in very advanced cases of glaucoma. This indicates that pattern-reversal VEP (at least that elicited with our stimulus) is not suitable for an early diagnosis of glaucomatous changes.

In contrast to pattern-reversal VEPs, the motion-onset VEPs exhibited much higher sensitivity for detection of glaucoma; their absolute latencies (not including the interocular differences) were increased in 72.5% of glaucomatous eyes. It has been shown that in glaucoma the nerve fibers belonging to the magnocellular pathway are affected earlier and to a greater extent [1, 2], which results in motion perception disorders described by several psychophysical studies [5, 7, 22]. Since the properties of the motion-onset VEP, especially its high contrast sensitivity [8] and low dependence on visual acuity [23], indicate that this type of VEP (particularly its dominant N160 peak) is probably of magnocellular pathway origin, the high sensitivity of motion-onset VEP in glaucoma could be predicted.

Occurrence of prolonged N160 peak latencies in very early glaucomatous visual field defects suggests that this test may be an appropriate method for objective assessment of early stages of glaucoma. The importance of the motion-onset VEP for the diagnosis of glaucoma is further supported by the fact that this type of VEP can be elicited in normal subjects by motion stimulation outside the central 40° of the retina. Moreover, its amplitude does not undergo any reduction if as much as the central 20° of the visual field is masked [24]. For this reason, the motion-onset VEP seems to be a convenient tool for objective perimetry, which might be useful especially in those patients in whom the large visual field defects (obtained by commonly used subjective perimetry) do not correlate with relatively small intraocular pressure and vague optic nerve head cupping findings. A selective stimulation of smaller

parts of the visual field at various eccentricities can increase the motion-onset VEP sensitivity because in full-field stimulation or stimulation restricted only to central or peripheral parts, the changed neuronal activity can be masked by normal VEPs from the unaffected parts of the retina (unpublished data). Objective perimetry based on the motion-onset VEP testing is a subject of our ongoing experiments.

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