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Abnormalities of voluntary saccades in Gilles de la Tourette's syndrome: pathophysiological consideration

Yoshiko Nomura[a,*], Hideki Fukuda[b], Yasuo Terao[c], Okihide Hikosaka[d], Masaya Segawa[a]

[a]*Segawa Neurological Clinic for Children, Tokyo, Japan*
[b]*National Institute of Industrial Health, Kawasaki, Japan*
[c]*Tokyo University, Department of Neurology, Tokyo, Japan*
[d]*National Eye Institute, National Institute of Health, Bethesda, MD, USA*

Abstract

Gilles de la Tourette's syndrome (TS) is a neurobehavioral disorder. Although the etiology and the pathophysiology of TS are still unknown, the involvement of the basal ganglia has long been postulated. On the other hand, saccadic eye movement was shown to be a useful measure to assess order and disorder of the function of the basal ganglia. To investigate the dysfunction of the basal ganglia of TS, we examined voluntary saccades in children with TS in comparison with the saccades in age-matched control children. Two kinds of saccades, visually-guided saccades (VGS) and memory-guided saccades (MGS) were evaluated. During the MGS, distracted saccades (DS), which indicate the distractibility, were examined. The results revealed the abnormalities in the parameters of the MGS, i.e. longer latencies and hypometric amplitudes, and decrease in the frequency of MGS. Whereas, the frequency of DS, the saccade to the predicted cue was significantly lower in younger patients (6–<9-years) than normal, but it was higher in the older TS children (9–<12-years). In addition, some of the patients showed large involuntary saccades, usually associated with eye blinks, during the task performance. These results suggest that in TS the basal ganglia fails to disinhibit the saccade neuron in the superior colliculus with the input of the frontal eye field to the striatum, and later allow the neurons to evoke non-goal directed saccades. In reference to abnormal saccades in other basal ganglia disorders with dopamine deficiency and to animal experiments with MPTP monkeys, these findings postulate primary hypodopaminergic state followed by upward regulation of dopamine receptors later in TS.

Keywords: Tourette's syndrome (TS); Voluntary saccades; Visually-guided saccades (VGS); Memory-guided saccades (MGS); Distracted saccades (DS); Involuntary eye movements

1. Introduction

Gilles de la Tourette's syndrome (TS) is the neurobehavioral disorder, often afflicting young subjects. Although there have been much progress in the field of clinical and basic sciences in this regard, the pathophysiology and etiology of TS are still not uncovered fully.

Clinical features of TS are characterized by the chronic motor and vocal tics which have the specific ages of onset, and sites of frequent involvement, i.e. most often starting with the eye blinking and abnormal movements of eyeballs.

Neurological, neuropharmacological and neurophysiological studies have suggested the involvement of the cortico-subcortical circuit, particularly the importance of the basal ganglia as the pathophysiology of TS [1].

To investigate the pathophysiology of TS, we performed the analyses of the saccadic eye movements of the patients with TS and compared with normal controls, because it is known that the basal ganglia contribute to the initiation and suppression of saccadic eye movements [2].

* Corresponding author: Yoshiko Nomura, Segawa Neurological Clinic for Children, 2-8 Surugadai Kanda Chiyoda-ku Tokyo 101-0062 Japan. Tel.: +81-3-3294-0371; Fax: +81-3-3294-0290.
E-mail address: nomura_y@kt.rim.or.jp

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2. Subjects

Among more than 1300 cases of TS patients who visited this clinic, 158 drug naive cases, 121 male and 37 female, underwent the investigation of the voluntary eye movements. As there are gender differences in the values of the parameters of the saccades, 121 and 79 drug naive male cases of TS were analysed in this study. The latter 79 cases were divided into two age groups; 6–<9-year-olds (23 cases) and 9–<12-year-olds (56 cases), and were compared with age matched normal controls, respectively.

3. Methods

The study was performed after obtaining the informed consent.

3.1. Eye movement recording

Eye movements were recorded using DC electro-oculography (EOG). In this study the horizontal eye movements were analysed with two electrodes placed on the lateral sides of the orbita. Besides these, eye blinks were monitored with the two electrodes placed above and below right eye.

The EOG signals, after amplified and filtered (low pass < 20 Hz), were fed into the computer at 500 Hz together with task-related events. The effect of the low-pass filtering was examined using sample saccades.

3.2. Apparatus

Small red spots of light were used for visual targets. They were presented with a dome-shaped black panel. The target was chosen by the signal from the computer out of 9 possible locations: eccentricities of 5, 10, 20, and 30 degrees in horizontal directions plus a central spot. At each location was a pinhole through which light was seen from a light-emitting diode (LED) located at the back of the panel.

3.3. Experimental procedure

The experimental room was dark except for a dim light at the back of the dome-shaped panel. The subjects sat in front of the panel with their head fixed on a chin rest. The height of the chin rest was adjusted so that the subject's eyes were approximately at the level of the center of the panel. Subjects held a micro-switch button which allowed them to initiate and terminate a task trial.

3.4. Behavioral paradigms

Three kinds of behavioral paradigms were used, following the procedures used for monkey experiments [3,4].

The saccade tasks were designed to induce visually-guided saccades (VGS) and memory-guided saccades (MGS). In VGS task, shortly after subjects pressed the button, a central spot of light came on upon which they were required to fixate. After a random period of time (1.2–2.0 s) the fixation spot went out and at the same time another spot (target point) came on, being presented randomly chosen by computer out of 8 positions (5, 10, 20, 30° horizontally from the central fixation point to right and left). Subjects were instructed to shift their gaze to the target as quickly as possible. After another random period of time the target became dim. Subjects had to release their finger from the button immediately after the dimming. If the button release was early enough (0.5–1.0 s), depending on the performance of individual subjects, a comfortable sound occurred to reinforce the subsequent performance of subjects. The goal-directed nature of this and the following tasks helped to maintain the alertness and volition of subjects. The eye movement made in this saccade task was a saccade guided by visual information derived from the target light.

MGS task was designed as follows. While subjects were fixating the central spot, another spot of light (target cue) was flashed (duration: 50 ms) to indicate the future location of the saccade target. Subjects were required to maintain fixation for another period of time until the fixation point went off. Subjects were asked to shift their gaze toward the remembered location of the target immediately after the fixation spot went off. The target came on 0.6 s after the fixation spot went off, randomly at variable eccentricities as in VGS task. The resultant saccade was therefore guided by visual spatial memory. Subjects could make a saccade after the onset of the target, as a visually-guided saccade, which however made it more difficult to detect the dimming of the target. Interestingly, most subjects were unaware of the difference between their own saccades, whether they were visually-guided or memory-guided. Subjects terminated each task trial by releasing the button in response to the dimming of the target, as in the VGS.

Another task was a visual detection task, which was designed to test the speed of visuo-manual information processing.

An experimental session was divided into five block, each comprising 20–25 trials: VGS task, MGS task, VGS task, MGS task, and visual detection task.

The results of visual detection task was not presented here, but the saccade to target during this task showed very similar results to the characteristics of distracted saccades (DS) (see below). However, it is not further discussed here.

3.5. Calibration of eye movements

Before the test session, we asked subjects to perform a task for eye movement calibration. This was the same as the saccade task, except that the target was presented at 20° to the right or to the left in an alternating manner. While subjects were performing the task, we adjusted the gain of the EOG so that the current eye position displayed on

the screen. EOG signals were found to be roughly linear so that the calibration was performed usually for 20°. To prevent possible changes of the gain of EOG during the test session, patients were adapted to the dim light condition for at least 10 min before starting the examination. EOG signals for vertical eye movements, however, were strongly non-linear and subject to artifacts due to eyelid movements. Therefore, vertical eye movements were examined only qualitatively. An eye blink was associated with a characteristic transient potential in vertical records, which we also examined.

3.6. Data analysis

The saccade analysed in the present study was the first saccade after each task event, i.e. offset of the fixation point, which was aimed at the visual or remembered target.

Parameters of saccade automatically detected by the computer were latency, amplitude, i.e. accuracy in amplitude, and peak velocity.

The amplitude of the saccade was evaluated as its ratio to the eccentricity of the target. The data only for distant targets (20 and 30°) were analysed because measurement errors in amplitude were thought to be too large for small saccades.

In addition, we evaluated if the saccade induced by the onset of the target cue, distracted saccades (DS), in the MGS. When the subject made a saccade to the target cue within 1000 ms of the cue onset, we determined that a DS occurred. When the subject made a saccade during the gap period of 600 ms (from the offset of the fixation point to the onset of the target), we determined that a MGS occurred. We then calculated for each subject the frequencies of DS and MGS as the percentage of trials in which these saccades occurred.

For the statistical analysis, the factors of ages (younger vs. older) and groups (normal control vs. TS) were tested by using two-way ANOVA.

4. Results

(1) An electro-oculogram recording of a case with TS in comparison with a normal control are shown in Fig. 1.

In the VGS task (left), control child made saccades to the currently visible targets with latencies usually between 200 and 250 ms. The saccades were fairly accurate for close targets (5–10°), but could be slightly hypometric for more distant targets (20–30°). In the MGS task (right), the normal control always made saccades to the remembered targets after offset of the central fixation point (solid vertical line) before the target actually came on (hatched vertical line). Their latencies from the offset of the fixation point were usually between 200 and 280 ms.

The recording of a TS subject (lower panel) was compared to the normal control (upper panel). The latencies of VGS did not show significant differences between TS and a control child. In contrast, the latencies of MGS were longer and more variable in the TS patient than in control subject. Saccades to the target sometimes occurred after the target came on, which were no longer MGS but VGS. In such trials, we judged that there was no MGS, and when MGS occurred, they were often hypometric.

The latencies of VGS increased with the target eccen-

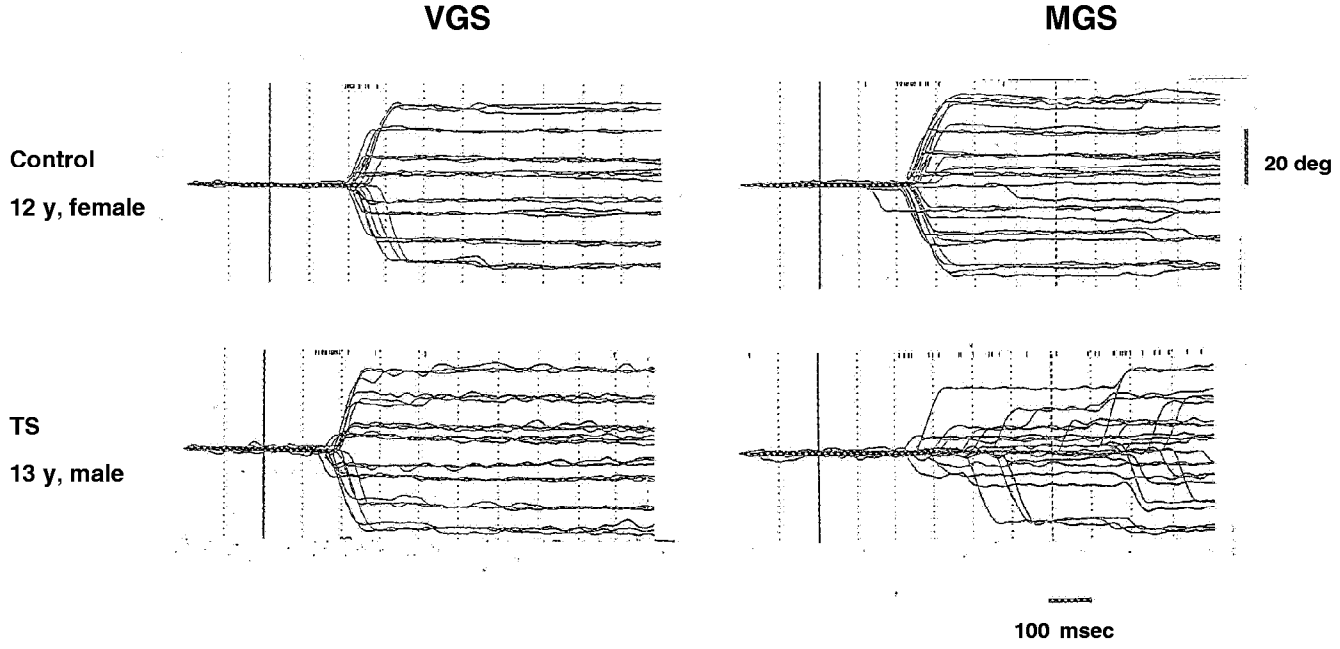

Fig. 1. Saccadic eye movements of a control and a TS subject. For both VGS and MGS, horizontal eye positions are superimposed for 25 consecutive trials. The saccade target was presented randomly out of 8 positions (5, 10, 20, 30°) horizontally from the central fixation point. Central fixation point: solid vertical line. Onset of a peripheral target point: hatched vertical line. Marks at top: onsets of saccades detected by the computer.

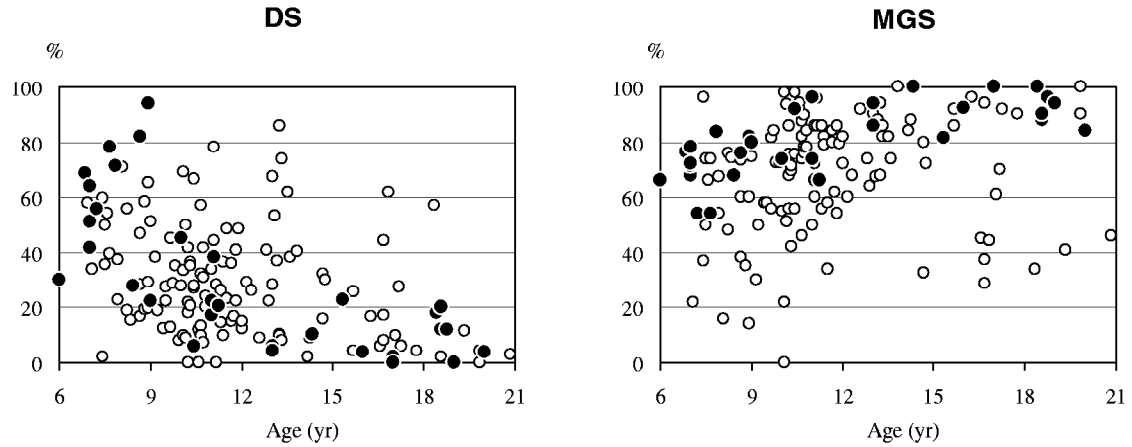

Fig. 2. Frequencies of DS and MGS in the wider age group. Open circles: TS patients, filled circles: normal controls.

tricities in both TS patient and the control subject. In contrast, the latencies of MGS tended to be shorter for more eccentric targets in both subjects.

(2) Overall data of 121 male TS patients with broader age range showed no differences in the latencies and amplitude of VGS in contrast to normal controls, but MGS were longer in latency and hypometric in amplitude. The frequencies of MGS and DS in TS patients showed variation of the data among individuals. In normal controls age-related decline in DS was present particularly before 9-year-olds, while MGS showed slow increase up to 12 to 15-year-olds (Fig. 2).

(3) The latencies of both controls and TS subjects with two age groups (6–<9 years and 9–<12 years) were longer for MGS than for VGS (Table 1).

The amplitudes of both saccades were hypometric in both TS and control subjects, which was more evident in MGS than VGS (Table 1). The amplitude of MGS tended to be more hypometric in TS than in controls (Table 1).

The statistical differences assessed by two-way ANOVA were significant with the factor of ages (6–<9-year-olds vs. 9–<12-year-olds) in latencies ($p = 0.048$) and amplitudes ($p = 0.016$) of MGS. As to the factor of groups (normal controls vs. TS), there was statistically significant differences in amplitudes ($p = 0.0451$) of MGS.

The peak velocities were faster in VGS than in MGS, but no differences were observed between TS patients and normal controls (Table 1).

(4) In addition to the differences in saccade parameters, more qualitative differences were found between TS patients and control subjects, especially in the frequencies of DS observed during MGS task.

The frequency of DS showed different patterns between two age groups of TS. In the younger group, it was less in TS than normal control, but increased in older TS patients (Table 1). In contrast, the frequency of MGS was less in TS patients than in control subjects in both age groups (Table 1). The differences of frequencies of DS were statistically significant in both factors, i.e. ages (6–<9-year-olds vs. 9–<12-year-olds; $p = 0.0001$) and groups (normal con-

Table 1
Parameters and frequency of saccades

	6–<9 years (younger children)		9–<12 years (older children)	
	control ($n = 12$) mean (s.d.)	TS ($n = 23$) mean (s.d.)	control ($n = 7$) mean (s.d.)	TS ($n = 56$) mean (s.d.)
Saccade parameters				
Latency (ms)				
VGS	252.4 (32.3)	256.1 (29.6)	248.4 (39.7)	251.1 (43.5)
MGS*	423.4 (67.3)	503.8 (133.6)	382.7 (93.5)	412.8 (111.0)
Amplitude (%)				
VGS	90.6 (6.4)	90.3 (5.8)	92.5 (7.7)	93.8 (5.6)
MGS*,†	77.9 (9.8)	71.3 (15.5)	84.0 (15.3)	78.8 (12.1)
Peak velocity (deg/s)				
VGS	420.4 (49.1)	408.7 (49.1)	401.1 (44.3)	411.7 (42.0)
MGS	339.2 (39.6)	328.1 (65.5)	327.7 (32.4)	332.1 (46.6)
Frequency of saccades (%)				
DS**,†	60.7 (20.3)	39.2 (19.4)	24.5 (13.0)	28.3 (17.3)
MGS	70.8 (9.6)	58.2 (22.2)	78.3 (11.9)	69.4 (20.0)

Age; $*p < 0.05$, $**p < 0.0001$. Group; $^{\dagger}p < 0.05$.

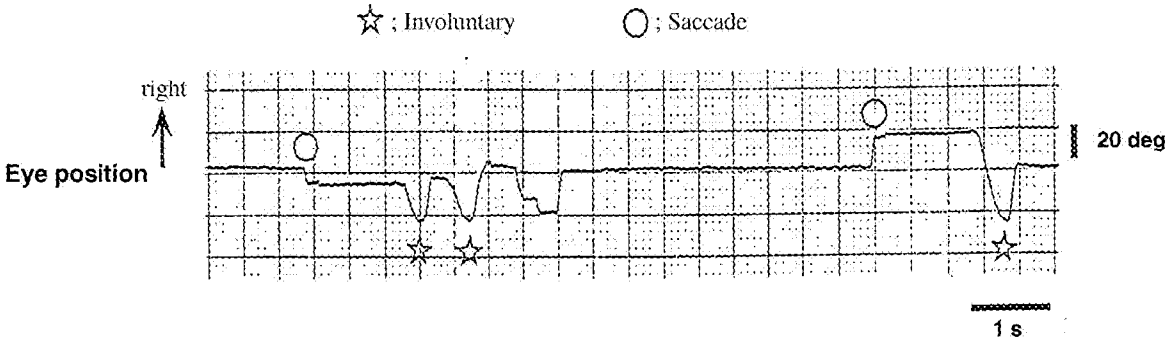

Fig. 3. Example of involuntary eye movements in a TS patient. Involuntary eye movements are indicated by stars; task-specific saccade by circles.

trols vs. TS; $p = 0.036$). There was also interaction between ages and groups ($p = 0.0074$).

(5) The majority of TS patients showed involuntary eye movements during the performance of saccade task as shown in Fig. 3. Involuntary eye movements were usually large saccadic shifts of eye position, frequently associated with eye blinks. Because of the associated eye blinks, it was sometimes difficult to observe actual eye movements on video records. The directions of these eye movements, judged from horizontal EOG data, were unilateral in some patients, while in others either to the right or left side.

5. Discussion

A goal-directed saccade results from the signal sent from the superior colliculus (SC) to brainstem saccade generators. The SC receives highly convergent inputs from the cortical and subcortical structures, and also from the substantia nigra pars reticulata (SNr). Thus, saccadic eye movements are under control of basal ganglia, and the direct and indirect pathways of basal ganglia work as disinhibition and enhanced inhibition onto the SC [2,5,6].

MPTP injected monkeys were studied for the saccades, and showed more difficulty in making MGS than VGS [7].

The saccadic task developed in monkey was applied to human [8,9], and the patients with basal ganglia disorders, particularly dopamine deficient state, were found to show making less MGS with longer latency and hypometric amplitude. They also easily break a fixation toward a visual cue [9–14]. Such impairments in initiation and suppression of saccades are thought to reflect the basal ganglia dysfunction; disinhibitory and inhibitory.

In view of the putative relationship of TS and basal ganglia dysfunction, we thought it to be very useful to apply the saccade tasks to these patients to understand its pathophysiology.

Many of TS patients were children, between 5 and 15 years old, the period during which oculomotor performances changed dramatically [15]. Therefore, it was particularly critical to compare TS children and control children by taking their development into account.

The present study on saccades of TS patients in contrast to the normal controls are summarized as follows.

MGS of TS patients were longer in latencies and hypometric in amplitude. TS patients were less likely to make MGS irrespective to their ages. These findings were similar to the findings of dopamine deficient disorders in human and MPTP monkeys, and implied the deficiency in initiating saccades based on memory.

DS occurred less frequently in TS patients under 9 years old, while they were more frequent in the older group. Thus our results implied that the distractibility in older children but not in younger, which suggested the deficiency in suppressing unnecessary saccades occurring in older TS subject. However, this may need further confirmation with a larger number of subjects.

The existence of distractibility in TS has shown to be controversial [16–18]. Bollen et al. [16] indicated that there was no tendency for TS patients to make saccades to irrelevant visual stimuli. However, the visual stimuli in their study were behaviorally irrelevant, while the visual stimuli in our study were behaviorally significant in that they indicated the future location of the saccade target.

The age related change observed in our study might indicate the dysfunction or distractibility taking place along with the development of the basal ganglia.

High distractibility observed in older patients is similar to the findings reported in patients with Huntington's disease [19]. We previously reported that patients with basal ganglia disorders, both with deficiency of the dopaminergic system and organic basal ganglia lesions with hypofunction of the indirect pathways, were likely to show abnormally high distractibility due to failure in suppression of the SC [12–14]. Those patients also had hypofunction of the direct pathways and showed difficulty in making MGS due to failure in inhibition of the efferent of the SNr [12–14].

The distractibility common to these basal ganglia disorders may be caused by insufficient inhibitory outputs of the basal ganglia.

This was demonstrated experimentally. A reversible blockade (injection of muscimol) of the monkey SNr, for example, produced irrepressible saccades to the side contralateral to the blockade [20]. This was because the

SC, a major recipient of the SNr, was released from the SNr-induced tonic inhibition and therefore emitted uncontrollable outputs.

A similar mechanism might explain the involuntary saccades observed in TS patients during the task.

In most cases the involuntary eye movements could not be observed because of associated eye blinks. However, careful examination of video records showed that both eyes made large saccadic shifts before the eyes were closed. Such blink-associated eye movements are unusual for normal subjects and in those cases the horizontal direction of such visible eye movements corresponded to the directions of horizontal EOG traces, and seemed to reflect the ocular tics. It has been demonstrated that normal eye blinks are associated with only small movements (usually less than 5°) [21]. Tic-like eye blinks in TS patients are unusual in that the eyes are closed forcefully and repetitively, unlike in normal subjects in which eye blinks occur spontaneously with more or less regular intervals.

The involuntary eye movements in TS patients were similar to those observed in monkeys which were injected with muscimol into the SNr. The SNr-induced irrepressible saccades were particularly robust when the monkey performed MGS and a visual stimulus was presented as the target cue, like the DS in TS patients.

These evidences observed in experimental animals suggest that in TS patients the SNr-induced inhibition over the SC might be insufficient, the same argument we made for the high distractibility of TS patients. Indeed, the patients who showed involuntary eye movements were more likely to break fixation by making DS and showed less MGS.

These lines of evidences including the results of the present study suggest that the inhibitory outputs of the basal ganglia are abnormally low in TS patients. These abnormalities in the oculo-motor basal ganglia circuits might be present in other basal ganglia circuits particularly in the non-motor basal ganglia thalamocortical circuit including limbic circuit, and might account for other symptoms seen in TS patients. While oculomotor symptoms are due to the insufficient inhibitory outputs of the SNr, non-oculomotor symptoms might be caused also by the insufficient inhibitory outputs of basal ganglia, that is of the GPi [22,23].

Furthermore age-related changes seen in the present study suggest the importance of the pathophysiological processes changing along with the functional maturation of the basal ganglia. It could be speculated that initially hypodopaminergic state causes decrease of MGS in younger group, but as ages advance, the developmental upward regulation of the dopamine receptors might cause the increased frequency of DS (see also Segawa, this issue).

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