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P300 endogen evoked potentials in somatization disorder: a controlled study

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Introduction. Somatization disorder (SD) is considered the most valid, reliable and consistent disorder over time from the entire group of somatoform disorders and the most disabling and expensive for the health system. The aim of this paper is to assess the discriminative, attentional and cognitive process in SD patients by auditory-stimulus P300 evoked potential.

Methods. Design: case-control study. Sample: cases group is made up of 25 patients, selected from the Miguel Servet University Hospital Somatoform Disorder Unit, that fulfill DSM-IV-TR criteria of SD using EPEP psychiatric interview. Twenty-five healthy and volunteer individuals without psychiatric or neurological disorders or history of disease were selected as control group. Both groups were matched by gender and age.

Results. Mean P300 latency was significantly ($p < 0.01$) higher in SD patients than in healthy people. The rest of variables studied (N100 latency, P200 latency, P300 amplitude in Pz) did not show any significant differences.

Conclusions. SD patients show electrophysiological disturbances in the cognitive process of information.

Key words:
Somatization disorder. Cognitive function. Evoked potential. P300.

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Potenciales evocados endógenos P300 en el trastorno de somatización: un estudio controlado

Introducción. El trastorno por somatización (TS) se considera la entidad más válida, fiable y consistente a lo largo del tiempo de todo el grupo de trastornos somatomorfos, así como el más invalidante y el que mayor gasto sanitario produce. El objetivo de este trabajo es evaluar el procesamiento cognitivo atencional y discriminativo en pacientes diagnosticados de trastorno de somatización mediante el registro del potencial P300 con estímulo auditivo.

Métodos. Diseño: estudio caso-control. Población: el grupo de casos esta formado por 25 pacientes, seleccionados de forma sucesiva, procedentes de la Unidad de Trastornos Somatomorfos del Hospital Universitario Miguel Servet de Zaragoza y diagnosticados de trastorno de somatización según criterios DSM-IV-TR mediante la Entrevista Psiquiátrica Estandarizada Polivalente (EPEP). Como grupo control se escogieron 25 sujetos sanos al azar, libres de patología psiquiátrica o neurológica, apareados por sexo y edad.

Resultados. Se observa que la media de latencia de P300 es significativamente superior ($p < 0,01$) en pacientes con trastorno de somatización respecto al grupo control. En el resto de variables estudiadas (latencia de N100, latencia de P200 y amplitud de P300 en Pz) no se observan diferencias entre los dos grupos.

Conclusiones. En los pacientes con TS existe una alteración electrofisiológica de los niveles del procesamiento cognitivo de la información.

Palabras clave:
Trastorno de somatización. Función cognitiva. Potenciales evocados. Onda P300.

INTRODUCTION

Somatization disorder is a relatively common disorder with 0.1 %-0.2 % prevalence in the general population and 5 % in primary care consultations[1]. It is diagnosed 10 times more frequently in the woman than in the man and usual onset age is generally from 15 to 20 years. Traditionally, it was thought that it was a disorder associated to low cultural and intellectual level but recent epidemiological studies have not verified this idea[1]. The somatization disorder is characterized by a pattern of multiple recurrent somatic symptoms over several years. The DSM–IV–TR[2] requires the disorder to have begun before 30 years of age. Traditionally, the clinical diagnosis was made by the presence of an elevated number of symptoms over the individual's

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lifetime. However, currently it is considered that the clinical nucleus of this disorder is not the number of physical problems but rather the fact that they affect multiple organs. Thus, the presence of the following criteria is required in the DSM-IV-TR[2]:

- Pain in at least four different body sites.
- At least two gastrointestinal symptoms other than the pain (nausea, abdominal distension, vomiting not related to pregnancy, diarrhea or food intolerance).
- Sexual or reproductive symptom other than pain.
- A pseudoneurological (or conversion) symptom other than pain.

All these symptoms cannot be explained by any medical disease. The somatization disorder is considered the most valid, reliable and consistent entity over time of all the somatoform disorder group[3]. It is also the most invalidating and that which produces the greatest health care cost.

Evoked potentials (EP) correspond with the variations of the nervous system brain electrical activity, excited by sensorial stimulus. They can be classified into exogenous evoked potentials, essentially dependent on the stimulation parameters, on into endogenous evoked potentials. The latter basically depends on the mental operations required for the task.

Evoked potential P300 is an endogenic potential that appears with a mean latency of 300 milliseconds, positive polarity amplitude and that generally has a maximum topographic distribution in zones of the middle line Cz and Pz (parietocentral). There are many studies on the location of those generated by the P300 wave. This wave is primarily the result of a cortical process. The amplitude reflects the synchronization of neuronal groups of brain structures that they are originated from. The intracortical recordings during the recording of this potential indicate that the production of the P300 wave is a cortical process produced from several generators activated by the task that the subject should perform and that spreads towards other cortical areas. It is admitted that the P300 wave comes from the production of post-synaptic potentials, mainly generated by activation of NMDA receptors, since the excitatory post-synaptic potentials originated in these receptors are long lasting and may contribute to the electrogenesis of long latency components, such as the P300.

Most of the paradigms used to evoke the P300 component are based on tasks that require the subject to maintain a high level of attention while they are performed. In these tasks, some stimuli are more significant and relevant (target stimuli) and appear less frequently than the other ones. In the auditory task, the subject receives 100 tones, 305 of which are higher (the infrequent) and 70% are lower (the frequent). The task that the subject should perform in the P300 potential consists in paying attention and counting the high tones, that is, the infrequent ones. Voluntary detection of infrequent stimulus in the sequence of frequent stimuli generates the P300 positive wave of great amplitude. This comes from the average of the brain electrical activity evoked by infrequent stimulus. The potential evoked by the frequent tone only has the typical N100 and P200 waves; negative wave that appears at around 100 ms after the stimulus and positive one that appears around 200 ms after the stimulus, respectively. The latency of P300 component provides an idea on the speed with which the subject can perform operations such as identify, discriminate, classify, categorize and obtain the relevant characteristics of a stimulus during a task. That is, the P300 component gives an estimation of the time needed for the stimulus to be perceived, identified and its subsequent classification. It is a measure of time sensitive to attention and working memory mechanisms.

The aim of this work is to evaluate objectively the cognitive, attentional and discrimative processing in patients diagnosed of Somatization Disorder according to the DSM-IV-TR criteria by recording of the P300 potential by auditory stimulus.

METHODS

Design

Case-control study.

Sample size

N = 25 individuals per group[4]. It has been calculated for p = 0.05; alpha: 80%; two tail, p (principle variable value, in this case, latency of P300 in the control group): 340 ms; q (difference in the intervention group of at least 10%).

Study population

Study group was formed by 25 patients, enrolled successively, from the Somatoform Disorders Unit of the Hospital Universitario Miguel Servet and diagnosed of Somatization Disorder according to DSM-IV-TR criteria. Twenty-five healthy subjects were randomly chosen. They had no psychiatric or neurological disease and voluntarily agreed to form a part of the study and were paired by gender and age (range of more/less 5 years). The study was approved by the Hospital's Ethics Committee.

Inclusion and exclusion criteria

Inclusion and exclusion criteria in table 1 were used for the somatization disorders group. Subjects older than or equal to 18 years, with no psychiatric and neurological di-

Table 1 Inclusion and exclusion criteria in the somatization disorders group

Inclusion criteria	Exclusion criteria
Age equal to or over 18 years	Age under 18 years
Elevated degree of motivation	Lacks motivation to complete the study
Somatoform disorder diagnosis made by a psychiatrist with the standardized polyvalent interview	Another psychiatric diagnosis on axis I (depressive disorder or anxiety disorder, history of substance abuse) or on axis II (personality disorder)
Fulfill the requirements for the neuropsychology evaluations: Concentration Understanding Motivation	Lack of reliability in performance of tests (simulation)
Spanish native language	Background of neurologic disorder

sease and without any background of both types of disease who voluntarily agreed to form a part of the study after signing the informed consent were included in the control group.

Instruments

- EPEP Interview: The SPPI (Standardized Polyvalent Psychiatric Interview) was used for the psychiatric diagnosis. This interview was developed for multiaxial psychiatric evaluation in patients with medical diseases.

- Evoked potentials method: The evoked cognitive P300 potential was recorded in each one of the subjects of the patient and control group by the application of *odd ball* paradigm type auditory stimulus application. Recording of the brain electrical activity was done in the international system of points 10-20 corresponding to Fz, Cz, Pz, C3, C4, P3 and P4, with electrodes of conventional surface, with referenced balance to both earlobes. The signal was acquired, amplified and filtered with the Track Walker system, version 2.0 (Neuronic®). Filters used were 0.5-30 Hz. Analysis time was 1.235 ms, including 100 ms prior to the stimulus. The signals were stored separately, obtaining an average, on the one hand, of those originated by the frequent stimulus and on the other, those generated by the infrequent ones. Eye movements were monitored with a recording referenced to the earlobes with electrodes on the external canthus of each eye. This made it possible to identify artifacts during the recording to be able to subsequently eliminate them. An average was obtained from a minimum of 20 responses for each type of stimulus.

Recording was done while the subject was sitting with his/her eyes closed. The patient was instructed to minimize eyelid and eyeball movement. Stimuli were delivered biaurally over headphones, using the *odd ball* paradigm as auditory stimulus type. Stimuli consisted of tones of 70 ms long and 70 dB SPL and 1000 Hz, for the frequent and 90 dB SPL and 2000 Hz for the infrequent, with a 70% and 30% likelihood of appearance, respectively, during 100 trials. The time interval between the onset of a stimulus and the onset of the next one was 1500 ms. The subject was instructed to identify the infrequent stimulus and mentally count the number of times that it appeared.

Variables studied

The waves recorded in each electrode and for each type of stimulus, both frequent and infrequent, were analyzed and latency of the P300 wave was defined as the latency to the point of maximum positive amplitude (non-inverted polarity) recorded in the electrodes of the middle line that appears after the exogenous components N100, P200 and N200, with a latency window between 200 and 450 ms. Amplitude was measured in regards to the pre-stimulus baseline. Latencies and amplitudes were also obtained for the N100 and P200 components in each one of the scalp sites described. We used the latencies of waves N100, P200 and P300 and the amplitude of wave P300 in site Pz of the scalp as variables for our study.

Statistical analysis

The statistical analysis was done with the SPSS 11.5 computer program for Windows. A descriptive analysis was performed for each study group using proportions for the qualitative variables and means with their standard deviations for the quantitative variables. We compared the variables between the two groups with the Student's *t* test for data following a normal distribution and the non-parametric Mann-Whitney U test for data that did not have a normal distribution.

RESULTS

The total sample was made up of 25 somatizing patients, 10 men and 15 women (40% and 60%, respectively), whose ages ranged from 30 to 65 years (mean age: 47 years; SD: 10.98) and 27 subjects that acted as a control group, 10 men and 15 women (15% and 25% respectively), with a mean age of 45 years (SD: 11.26). There were no significant differences regarding age, as was to be expected, from the pairing procedure.

The auditory evoked potentials recorded in the middle line for the frequent stimulus included the N100-P200-N200 complex. The values of these for the latencies of N100 and

P200 components for each one of the groups are shown in table 2.

After infrequent stimulus, auditory evoked potentials formed by the N100-P200 complex, followed by the appearance of the P300 wave, whose latency and amplitude in site Pz for both groups are shown in table 3, were recorded. (The mean amplitude of the P300 wave was maximum in site Pz of the scalp). The results are expressed as means with their standard deviations, with 95% confidence intervals for the mean and with minimum, maximum and median values.

Figure 1 shows a characteristic example of a control subject, with the responses obtained in the different scalp sites. The different components of the potential evoked by the frequent and infrequent stimulus, the thin line corresponding to the response generated by the frequent stimulus and the thick one to that generated by the infrequent one, are observed. The time when the application of the stimulus is indicated is latency time 0 after which the latency of the potential components is quantified. Analysis time is 1.235 ms and includes the 100 ms prior to the stimulus and the sensitivity is 4.5 mV. Response evoked by the infrequent stimulus in the Pz location of the scalp where the P300 wave has a maximum amplitude is shown in red. The first cursor indicates the latency of the N100 wave, the second the latency of the P200 wave and the third the latency of the P300 wave. P300 latency value appears in the upper part of the recording.

Table 2 Latency values (in ms) of the N100 and P200 waves generated after application of both frequent and infrequent stimulus for both study goups

	N100 latency (ms)	P200 latency (ms)
Patients		
Mean ± standard deviation	128.50 ± 18.517	224.48 ± 31.802
95% CI for mean	(119.83-137.17)	(210-238.95)
Median	129	218
Minimum value	94	167
Maximum value	165	293
Controls		
Mean ± standard deviation	128.63 ± 11.084	233.15 ± 33.775
95% CI for the mean	(124.24-133.01)	(219.51-246.80)
Median	128	224.50
Minimum value	111	178
Maximum value	155	342

Table 3 Latency values (in ms) and amplitude (in μV) of the P300 wave generated after application of the infrequent stimulus in both study groups

	P300 latency (ms)	P300 Pz amplitude (μV)
Patients		
Mean ± standard deviation	374.67 ± 32.426	11.65 ± 4.030
95% CI for mean	(358.09-391.25)	(9.76-13.54)
Median	36.426	12,00
Minimum value	310	3
Maximum value	445	19
Controls		
Mean ± standard deviation	341.70 ± 25.790	12.52 ± 2.679
95% CI for the mean	(331.50-351.91)	(11.41-13.63)
Median	339	13
Minimum value	300	7
Maximum value	400	18

Figure 2 corresponds to an example of a subject from the patient group diagnosed of somatization disorder. It shows a correct configuration of the responses evoked after the frequent stimulus (thin line) and infrequent one (thick line). P300 amplitude in Pz location and latencies of N100 and P200 waves have a similar value to the recordings of the control group. On the contrary, the P300 wave latency appears to be delayed regarding that observed in the control group.

Mean latency of the P300 wave in the patient group diagnosed of somatization disorder was 374.67 ± 36.426 ms (95% confidence interval between 358.09 and 391.25 ms). In the control group, it was 341.70 ± 25.790 ms (95% confidence interval 331.50 and 351.91 ms). Using the statistical analysis, we observed statistically significant differences ($p < 0.01$) in regards to the mean P300 latency between both groups, showing a significantly greater latency in the patient group diagnosed of somatization disorder versus the control group.

Figure 3 shows the statistical values of the P300 latency variable in both groups, where the difference between them can be observed.

We observed no significant differences between both groups in the remaining variables studied (N100 latency, P200 latency and P300 amplitude in Pz). Furthermore, we observed no significant differences of the variables studied in regards to gender in both groups.

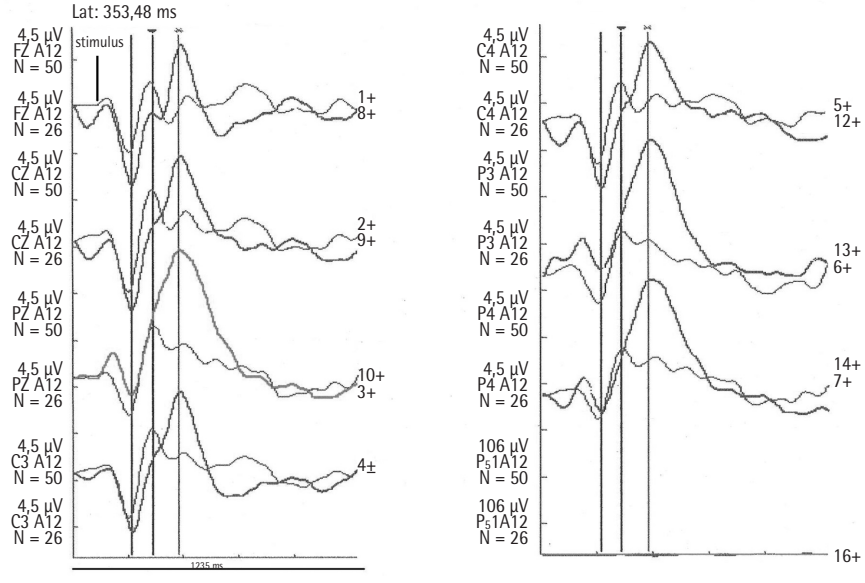

Figure 1 *Example of a recording in a control group subject. The different components of potential evoked by the frequent and infrequent stimulus in the different scalp sites, the thin line corresponding to the response generated by the frequent stimulus and the thick one to that generated by the infrequent one. The time when the stimulus was applied is indicated. Analysis time is 1,235 ms and includes the 100 ms prior to the stimulus and the sensitivity is 4.5 µV. Response evoked by the infrequent stimulus in the Pz site of the scalp, where the P300 wave has a maximum amplitude. The first cursor indicates the N100 wave latency, the second the P200 wave latency and the third the P300 wave latency. The P300 latency value appears in the upper part of the recording.*

DISCUSSION

The recording of the P300 potential makes it possible to observe the changes in electrical brain activity associated to the processing of a stimulus and has been widely used in the literature to evaluate the patient's cognitive capacity. There are many studies of P300 potential in psychiatric diseases, such as attention and learning disorders, schizophrenia, dementia and manic-depressive disorder, among others. However, there are no studies in patients diagnosed of somatoform disorders.

Although patients diagnosed of somatization disorder frequently report neuropsychological disorders (difficulties to maintain attention, problems related with short term memory, etc.), there is presently only one study aimed at evaluating the reach of that fact[6]. Six patients diagnosed of somatization disorder, 4 diagnosed of undifferentiated somatoform disorder and a control group of ten healthy women (without a history of chronic physical or psychiatric disease) participated in that study. Somatizing patients did not have psychiatric comorbidity in axis I. The cognitive function of these patients was evaluated with different neuropsychological instruments (Mild Deterioration Battery (MDB), WAIS scale: similarities, numbers, digits and cube keys, associated pairs of words; remembering objects, Benton Visual Retention Scale, Wisconsin Card Sorting Test (WCST), Stroop), controlling age and years of schooling. The results found showed worse performance (statistically significant) of the patients with somatization disorder and undifferentiated somatoform disorder in the execution of the cube tests, similarities and processing speed. The results of this study suggest that somatization is associated with a brain dysfunction, especially in regards to the control of attention and memory.

Neuroimaging studies show changes in brain metabolism in patients with severe somatization, with lower rates of brain metabolism of glucose in both caudate nuclei, right putamen and left precentral gryus, compared with the healthy controls[7] and hypoperfusion in the unilateral or bilateral brain SPECT in different brain areas[8]. We should use theories formulated from the cognitive-behavioral orientation to explain the interaction between physiological, cognitive, emotional and behavioral processes.

In the case of somatization disorders, the patients have physiological arousal higher levels, which prevents them from becoming used to the stressful stimuli, maintaining the stress response longer than into those who do not have this disorder[9]. This physiological arousal is translated in the amplification of the intensity of the sematosensorial stimuli. This causes the patients to experience their body sensations as harmful, threatening and painful. Furthermore, the patients interpret these sensations as malignant, believing that they are a sign that they suffer a serious disease and tending

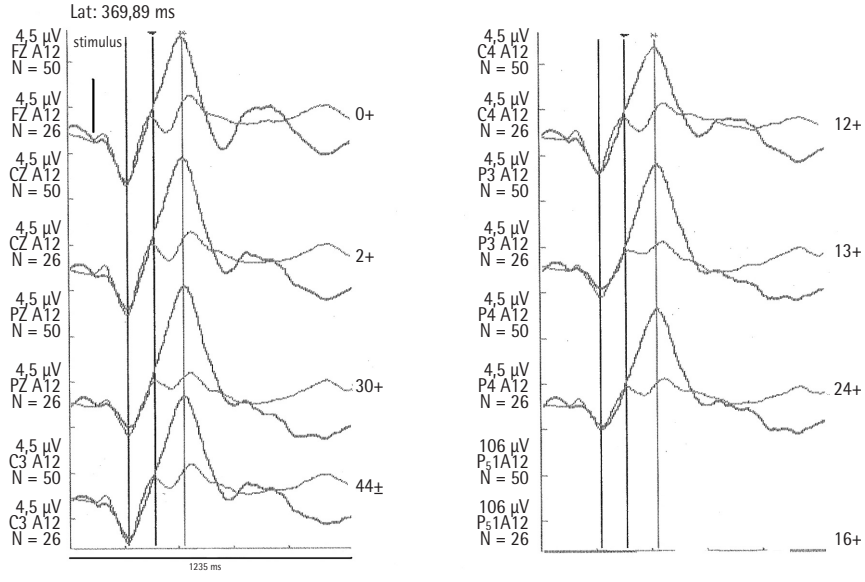

Figure 2 *Example of a recording of a subject from the patient group diagnosed of somatization disorder. Correct configuration of the responses evoked after frequent stimulus (thin line) and infrequent one (thick line) for each scalp location is observed. Amplitude of P300 in Pz location and latencies of N100 and P200 waves have a similar value to those recorded in the control group, on the contrary to the P300 wave latency that appears delayed.*

to catastrophism. Distorted thoughts arising in regards to body sensations are translated into unadaptive behaviors, such as seeking multiple treatments, adoption of the role of patient, decreased participation in social and/or family activities and low work performance, even becoming incapacitated. These distorted thoughts produce anxiety and depression, disorders that newly increase the physiological arousal. This leads to the maintenance of the stress response and thus the vicious circle that is created in these disorders.

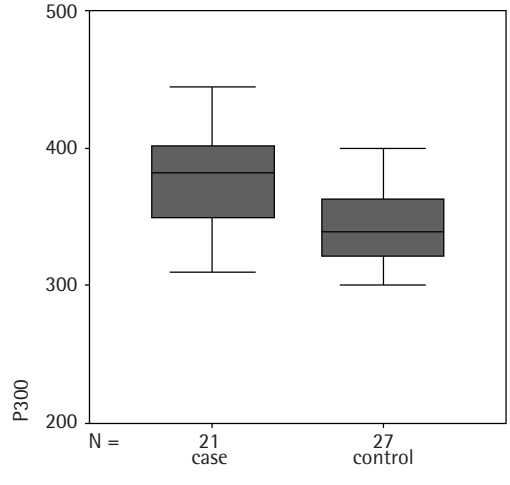

Figure 3 *Chart of the median value of P300 latency and 50 % of the values studied in both study groups.*

If we keep in mind that the endogenous EP, such as the P300 component, are electrophysiological correlates of the cognitive information processing, alteration in some of the cognitive processing levels should be reflected by an abnormality in these EP. In this study, the patients diagnosed of somatization disorder have had an increased P300 potential latency, with significant differences, regarding the control group. This implies that there is an electrophysiological alteration of the cognitive processing levels of the information.

Cognitive functions involved in the generation of this potential are attention and memory. During task performance, the patient should pay attention and memorize the stimulus that he/she must respond to, that is, the short term memory or operative memory (capacity to maintain the information on the first level) is assessed. This increase in latency of the appearance of the P300 component is translated into a decrease in the speed of identifying and classifying the stimulus during the task. As we have seen, according to the cognitive-behavior model, the somatizing patients have high levels of hypervigilance to physical sensations and to automatic thoughts that interpret these sensations. This hypervigilance to internal stimuli could be translated into problems of attention and short term memory such as those obtained in the analysis of the P300 latency.

There are multiple generators of the P300 potential. The correlation of the results obtained in the surface recordings and recordings in depth orient towards locating these generators from the medial part of the temporal lobe of both hemispheres, the hippocampus, amygdala and to a certain degree the frontal lobes and posterior parietal cortex being

involved. The P300 wave is generated by postsynaptic potentials produced by activation of the NMDA receptors. These receptors, besides being very abundant in the central nervous system, are involved in many functions, some of them very important for the good functioning of the brain functioning such as learning or memory while they are other times involved in mechanisms of brain death or diseases such as epilepsies. One of the processes where the NMDA receptors play a key role is synaptic plasticity. This synaptic plasticity participates in the maturation of the nerve circuits not only during development but also in the adult. One form of synaptic plasticity is the long term potentiation that is at the base of the attention and memory processes.

The P300 component amplitude refers to the magnitude of the electrical field that has been generated in a certain time as a result of the specific neuronal activity during the information processing of a stimulus and is determined by the number of neurons involved in this activation. This amplitude depends on the synchronization of neuronal groups, of brain structures related with their generation. On the contrary to that observed in the P300 latency, we have not found any differences in the amplitude of the wave generated in the patients diagnosed of Somatization Disorder regarding the control group. This would mean that there is no lack of organization, integration and synchronization of the brain circuits related with their generation.

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