

Comparison of The Neurocognitive Skills Between Generalized Anxiety Disorder and Premenstrual Dysphoric Disorder Patients: A Controlled Study

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Abstract

Background: This study aimed to evaluate and compare the effects of the cyclic reproductive hormonal changes on neurocognitive functions in the female of childbearing age. In the study, Generalized Anxiety disorder (GAD) patients and Premenstrual Dysphoric Disorder (PMDD) patients were compared with the healthy controls.

Methods: One of the two psychiatric samples was the group of GAD (n = 38) which had 20 and higher on Hamilton Anxiety Scale (HAM-A) score and the other was the group of PMDD (n = 48). Age matched healthy control group (n = 42) was also included into the study. Venous blood samples were taken twice for hormonal assays according to the menstrual phases. Frontal assessment battery, stroop test, and weschler verbal memory tests were also applied for the evaluation of neurocognitive changes with respect to menstrual phases.

Results: Taken together with the repeated measures and the data analysis, the GAD group had significantly worse performance regarding overall neurocognitive functions (particularly memory skills, attention and psychomotor function) in their late luteal phase compared to the PMDD group. The control group had significantly better performance than the other two groups. Additionally, cyclic hormonal change rates of the both patient groups were significantly higher throughout the menstrual cycle than the control group.

Conclusions: Previous studies indicate PMDD patients suffer from some neurocognitive impairment during late luteal phase due to the central role of female reproductive hormones. However, this study finds GAD patients had worse neurocognitive impairments than the PMDD patients. Therefore, further research should be conducted on complex information processing which involved in GAD patients.

Keywords: Neurocognitive functions; Premenstrual dysphoric disorder; Generalized anxiety disorder; Female reproduction hormones

Introduction

Premenstrual Syndrome (PMS) is a complex disorder characterized by recurrences of negative behavioral, psychological, and physical symptoms appearing in luteal phase (following ovulation) and resolving in follicular phase of the menstrual cycle [1-4]. Forty percent of women in reproductive age suffer from some PMS symptoms of sufficient severity to interfere with some aspects of their lives, while 3-9% of women cannot continue their daily functions due to symptoms and get the diagnosis of premenstrual dysphoric disorder (PMDD). Thus, the Premenstrual Dysphoric Disorder (PMDD) is an important cause of psychological and physical stress for female of reproductive age [5,6]. PMDD is characterized by various mood symptoms. Particularly, five or more of the symptoms including irritability, inattentiveness, depression, stress, malaise, repugnance, seediness, anxiety, and fatigue must be present during luteal phase [7]. The diagnosis of PMDD can be put only by a prospective follow up of symptoms during consecutive two menstrual cycles. These symptoms should be observed during the last week of the luteal phase (premenstrual), subside with the beginning of the menstruation, and end with follicular phase (pre-ovulation). The dramatic cyclic alterations in mood of women with PMDD have been reported both clinically and in research studies [7-10]. In addition to mood disorders during luteal phase, women with PMDD also report subjective disorders in cognitive functions such as attention, concentration, memory, and motor coordination, decreasing their efficiency by interfering with daily productivities [9,10]. On the other hand, no detailed study on which aspects of psychomotor and cognitive performance of women with PMDD deteriorate during luteal phase

exists, and the results of other studies are inconsistent [7-9]. It is unclear whether these complaints are due to an actual cognitive decline or some other subjective factors such as negative referral to the environmental stressors related to the menstrual phase.

Generalized Anxiety Disorder (GAD) has been defined as the presence of at least three out of six symptoms as excessive anxiety related to many events or activities (such as professional or scholar success) or sadness (expectations of concern, having difficulty in controlling anxiety and sadness, nervousness, and agitation), easy fatigability, lack of concentration, irritability, muscle strain (tension), and disordered sleep [11]. Since GAD frequently accompanies major depression, dysthymia, panic disorder, and drug abuse, it is difficult to ascertain the difference between normal anxiety and GAD, and to make diagnosis. It has been reported that, after the exclusion of concomitant panic disorder and major depression, the annual prevalence of GAD is 1.7 -3.1% and its life-time prevalence is 4.1- 6.6%. It is two times more prevalent in women than men, and average time of diagnosis is the early 20's.

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Although GAD and PMDD are based on different etiologies and classified under different diagnostic categories, they present with similar symptoms in some extent. GAD distorts patient's functionality, professional performance, and worsens the quality of life. There are scarcely any studies on the differences arising in cognitive processes in GAD and their effect on clinical picture.

Previous studies indicate that GAD is a separate entity from other anxiety disorders and constitutes one of the most frequent forms. It has also been understood that the genetic predisposition of GAD is different from other anxiety disorders. Anxiety cognitively affects person's thought, attention, perception, and learning skills. There may be concentration difficulties. Apart from DSM-IV diagnostic category, GAD symptoms may be discussed in three categories; 1) excessive physical stimulation (muscle tension, nervousness, fatigue, anxiety, insomnia), 2) falsifying in cognitive processes (anxiety, unreal problem handling, inability to direct attention) 3) poor coping skills (avoidance, lack of problem solving skills, postponing responsibilities).

On the other hand, periodic hormonal alterations regulating menstrual cycle exert important biological effects on female body by multiple physical pathways [12]. Estrogen starts or mediates important biological functions via its receptors detected in many tissues and cell types. Indeed, fluctuations in estrogen levels have physiologically demonstrable effects almost on every organ system in human body [13]. Studies in the past two decades confirm that estrogen has a potential effect on neurocognitive processes and its receptors are widespread in the brain [14]. Estrogen exerts its effects in many different levels (genomic and beyond) in central nervous system. It has the ability to influence electrical excitability, synaptic functions, and neurotransmitter production by alteration of morphologic features of neural elements functioning in nervous system [15]. It has been demonstrated that estrogen influences many neurotransmitter systems including dopaminergic, serotonergic, cholinergic, and GABAergic systems [16].

The information processing system in human brain is a complex and multi-factorial process comprising attention, learning, memory, model recognition, problem solving, language processing, abstract intellectual process, and psychomotor abilities [7-9]. Although frontal lobe is presumed to be responsible for executive functions, it has been observed that executive functions are also deteriorated in lesions of non-frontal subcortical structures such as striatum and thalamus [17,18]. Data from the animal studies suggests that memory reinforcement takes place in hippocampus [16,15]. It has been showed that estrogen, in addition to accelerating short-term memory, influences cyclic changes in hippocampus [8-10]. It is known that estrogen receptors in human brain are present in largest concentrations in hypothalamus, amygdala, and hippocampus [13,14]. Many studies on perceptual, motor, and cognitive performance related to menstrual cyclic phases in asymptomatic women have reported no significant phasic differences. The only study defining cyclic differences was reported by Hampson and Kimura and used spatial rotation and manipulation tests. Women have a better performance in verbal fluency whereas a poorer in spatial orientation in mid-cycle when estrogen predominates. There are too few studies evaluating cognitive functionality in women with premenstrual syndrome.

This study aims to explore the effects of hormonal changes during menstrual cycle on cognitive functions (especially attention, concentration, memory, abstracting and motor coordination) in female of reproductive age and to compare patients with PMDD and patients with GAD in terms of neurocognitive abilities in menstrual phases.

Methods

Subjects

A total of 50 patients with diagnosis of premenstrual dysphoric disorder (PMDD) and 40 patients with diagnosis of generalized anxiety disorder (GAD) without PMDD were recruited from Erenköy Mental Hospital Outpatient Treatment Center between January 2011 and July 2011. A healthy age and education matched control group consisting of 45 women was also recruited for comparison. All participants were diagnostically interviewed as part of the intake to meet entrance criteria 17 participants were excluded from the study because of their unattendance, pregnancy and some other medical problems. Eventually, (n=38) GAD patients, (n=48) PMDD patients and (n=42) healthy control remained. All participants were given informed consent and the study was approved by the local institution of review board. The following inclusion criteria were prerequisites to be present for all participants for the last 6 months and during study period: 1) having regular menstrual periods, 2) taking no hormone, vitamin, or antiaging drugs, 3) not being pregnant, 4) being of 18-45 years old, 5) having normal gynecologic and general physical examination findings, 6) not using hormonal implant, injection, or intrauterine device, 7) not having any endocrinologic disorder, 8) for GAD patients, having a HAM-A score of equal or greater than 20.

Study design

At the beginning of the study, we assume that "good" plus "very good" rates of Frontal Assessment Battery (FAB) scores in the healthy control group would be above 90 %. Also we suppose that "good" plus "very good" rates of Frontal Assessment Battery (FAB) scores in the GAD and PMDD groups would be below 60 %. By this supposition, 25 case numbers was determined with the 80 % power and 5 % margin of error. We reached the ~ 40 case numbers easily. At the beginning of the study, all patients and control group were interviewed diagnostically and also Premenstrual Syndrome Assessment Scale was given. All participants were interviewed 5 times by study protocol and vital signs of participants were recorded in each visit.

Visit 1 An informed consent form was obtained from the participant after providing sufficient information on the study. The application of daily rating form (DRF) was explained. In addition, by filling sociodemographic form of the participant a follow-up appointment for the second visit appropriate for menstrual cycle was made.

Visit 2 (Month 1, follicular phase, day 8-14): Venous blood was drawn for laboratory examinations. DRF points were checked and feedback was given. All participants underwent Frontal Assessment Battery, Stroop test, Weschler Verbal Memory Scale at this visit.

Visit 3 (Month 1, luteal phase, day 21-26): Venous blood was drawn for laboratory examinations. DRF points were checked.

Visit 4 (Month 2, follicular phase, day 8-14): DRF points were checked and feedback was given.

Visit 5 (Month 2, luteal phase, day 21-28): Vital signs were recorded and DRF points were checked. During this visit participants underwent Frontal Battery, Stroop Test, and Weschler Verbal Memory Scale. Participants were informed to continue DRF records until 3-5th days of their next menstrual cycle and to hand them in to the researchers.

Measurements

In order to scan participants for PMDD all participants initially underwent Premenstrual Assessment Form (PAF), a self-reporting

retrospective questionnaire related to mood, behavior changes, and physical signs for the preceding three menstrual cycles [19]. To rule out or in PMDD all participants also filled in Daily Rating Form (DRF) every evening during at least two cycles preceding the study [20]. Ovulation follow up was done by ear thermometers. Venous blood was drawn twice for hormone level determination according to the menstrual phases. In addition, frontal battery, stroop test, weschler verbal memory scale tests were chosen to assess neurocognitive changes during follicular and late luteal phases. These cognitive instruments are practical and easy to use for clinical researches. Also validation and reliability studies for Turkish versions of these tests are available. Frontal assessment battery is a brief and easy-to-apply battery composing of six tests enabling rapid review of frontal lobe functions such as cognitive and behavioral executive functions [21]. Of these subtests “similarities” explores abstraction and conceptualization, “phonologic verbal fluency” explores mental flexibility, “motor series” explores motor planning, “conflicting instructions” explores sensitivity to interference, “go-no go” explores inhibitory control, and “prehension behavior” explores environmental autonomy. Its application lasts approximately 10-15 minutes. Every subtest is given 0-3 points. Total points possible equals to 18. Stroop test typically assesses selective attention and concentration ability of patients and can be applied in 5-10 minutes [22]. Weschler memory scale was developed by Weschler [22] and revised later. It has verbal and performance parts and consists of seven subscales. The sum of all subscores is translated into the standart score. In this way, the revised memory score of an individual would be available. By the aim of a second table, revised memory score according to age. Validation and reliability study for Turkish version of Stroop test and Weschler memory scale was made by Karakas et al. [23].

Statistical method

Data were analyzed with SPSS 19.0 (SPSS Inc, Chicago) package software after being transferred to computer environment. Frequency, ratio, mean, and standard deviation were used as descriptive statistics.

	Healthy control	PMDD	GAD	p
	Mean ± s.d	Mean ± s.d.	Mean ± s.d.	
BMI	22.67 2.99	22.26 ± 3.51	25.71 ± 5.19	0.025
Menache Age	13.31 ± 1.14	13.34 ± 2.31	12.42 ± 1.03	0.007
Mens.Period(Day)	5.02 ± 1.27	4.93 ± 2.00	6.42 ± 2.18	0.001
PAF	149.74 28.17	285.57 ± 70.11	260.34 ± 57.15	0.000

ANOVA/ Tukey test/ t test/ Krusval Wallis/ mann-Whitney u test/ 95% confidence interval

Table 1: Group comparisons by means of body mass index (BMI), menarche age, menstruation period and Premenstrual Assessment Form (PAF) total score.

		Healthy Control		PMDD		GAD		Chi-Square	p
		n	%	n	%	n	%		
Luteal verbal memory score	Very good	27	64.3%	0	0.0%	0	0.0%	87.27	0.000
	Good	13	31.0%	16	33.3%	14	36.8%		
	Average	2	4.8%	26	54.2%	12	31.6%		
	Bad	0	0.0%	6	12.5%	12	31.6%		
Follicular verbal memory score	Very good	42	100,0%	23	47.9%	16	42.1%	39.34	0.000
	Good	0	0.0%	23	47.9%	22	57.9%		
	Bad	0	0.0%	2	4.2%	0	0.0%		
Luteal and follicular phase difference	z	-3.690		-5.096		-4.697			
	p	0.000		0.000		0.000			

Chi-square/ Wilcoxon test/ 95% confidence interval

Table 2: The distribution of weschler verbal memory scores of sample groups in terms of menstrual phases. Those with a Weshler total score of 135 or higher are classified as “very good”, 120-135 as “good”, 95-120 as “average”, and 95< as “bad” (P< 0.0001).

The normality of the data was tested by Kolmogorov-Smirnov test. Parametric discontinuous data were analyzed by ANOVA (Tukey test in sub-analyses). Non-parametric data were analyzed by Kruskal-Wallis test and sub-analyses were obtained by Mann-Whitney-U test. Wilcoxon test was used to analyze repetitive measurements. Proportional data were analyzed by Chi-Square test or Fischer Exact test unless Chi-Square requirements were met. Statistical significance was accepted as a p level of < 0,05.

Results

All women had an ovulatory menstrual cycle of 26-32 days long. The mean age was (Mean ± standard deviation) (29.77 ± 6.47) in PMDD, (32.32 ± 4.48) in GAD and (30.95 ± 4.59) in healthy controls. There were no significant differences regarding socio-demographic data like age, marital status, number of pregnancy and birth, education, and economic level. The group with anxiety disorder had a higher BMI than healthy controls and PMS group (p<0.05). Menarche age of PMS group was significantly higher than that of healthy group (p<0.05). The group with anxiety disorder had a longer bleeding time compared to healthy and PMS groups (p<0.05). Premenstrual assessment form scores of healthy control group were significantly lower than GAD and PMS groups (p<0.05) (Table 1).

There were no significant differences between groups regarding socio-demographic data, blood pressure, follicular phase oxygen E, and luteal phase cortisol levels. GAD group had a significantly lower (36.49 ± 31.95) Luteal estrogen level compared to healthy controls (117.21 ± 99.13) and PMDD group (103.94±127.02) (p<0.05). GAD group had a significantly higher follicular progesterone level (4.81 ± 1.74) than healthy (2.96 ± 3.87) and PMDD (3.11 ± 2.94) groups. GAD group had a significantly lower luteal progesterone level (3.78 ± 2.92) compared to healthy control group (7.23 ± 5.95). GAD group had a significantly lower follicular cortisol level (6.32 ± 3.17) compared to healthy controls (9.22 ± 4.64) and PMDD group (11.16 ± 4.83) (p<0.05). Stroop test performance of the healthy group was higher than two patient groups yet did not reach significance.

The distribution of the Weshler Verbal Memory Scale scores in healthy and patient groups in terms of menstrual phases Table 2. Healthy group had significantly higher luteal memory scores compared to PMDD and GAD groups (p<0.05). GAD group had significantly lower luteal verbal memory scores compared to PMDD group (p<0.05). Healthy group had significantly higher follicular verbal memory scores than PMDD and GAD groups (p<0.05). Follicular phase verbal memory scores were significantly higher than luteal phase verbal memory points in all three groups (p<0.05) as shown in Figure 1.

Follicular phase frontal test scores were significantly higher than luteal phase frontal test scores in all three groups ($p < 0.05$). As seen in Table 3, healthy group had significantly higher frontal test scores in both follicular and luteal phases compared to PMDD and GAD groups ($p < 0.05$). Furthermore, PMDD group had significantly higher follicular and luteal phase frontal test scores than GAD group ($p < 0.05$). Figure 2 indicates percent ratios of frontal assessment battery test scores of PMDD, GAD, and healthy control groups by the phases of menstrual cycle.

Discussion

This study is the first study in which the effects of hormonal changes of menstrual cycle on neurocognitive functions in patients with premenstrual dysphoric disorder and generalized anxiety disorder are compared with those of a healthy control group. There are many studies comparing cognitive abilities of PMDD patients with healthy

controls or patients with depression. The interpretation of PMDD as a mood disorder subtype plays an important role in this regard. However, to our knowledge there are no studies in literature comparing patients with PMDD and GAD in terms of neurocognitive abilities.

The primary result of this study was that the GAD group had a significantly worse performance than PMDD group in terms of neurocognitive functions (particularly verbal memory, verbal fluency, and psychomotor abilities) in late luteal phase. Healthy control group had a significantly better performance than both patient groups in all cognitive process tests.

Neurocognitive abilities are mental processes such as problem solving, abstraction, reasoning, remembering, symbolizing, and apprehension, inference, planning, and understanding a language. Supervisory functions comprise a vast spectrum of neurocognitive abilities enabling one to become independent, goal-oriented and to direct his/her attitudes on their own. Frontal lobe is largely responsible for supervisory functions. Complexities in processing and programming are related to frontal lobe disorders.

Previous studies comparing cognitive functional performances of PMDD patients in terms of menstrual phases yielded different results. In some studies it has been detected that there is a modestly significant performance drop or no change at all in luteal phase in some individual tasks. Some other studies found that verbal recall performance deteriorates in women with PMDD than without. However, the deterioration was independent of the phases of the menstrual cycle [7]. Similarly, another study examining cognitive functions in women with PMDD concluded that these patients do not have significant frontal lobe cognitive or attention deficit and a biopsychosocial explanation, developed for increased reactivity and the change in self-sense seen in menstrual period, may explain subjective cognitive signs [10,24]. In another study, women with PMDD exhibited more psychomotor slowing in luteal phase compared to follicular phase [9]. Although the decreased performance in neurocognitive abilities observed in women with PMDD partly results from dysphoric mood in late luteal phase, it appears that neurocognitive impairments basically stems from some independent physiologic and psychoneurologic processes in which female reproductive hormones play a central role. Women with PMDD have an increased sensitivity to environmental alterations and cycles. This sensitivity appears as subjective cognitive and behavioral symptoms as a response to a series of events in hypothalamic-pituitary-gonadal axis [10].

According to the findings of this study, the worse performance of patients with GAD than the PMDD group in all tests measuring

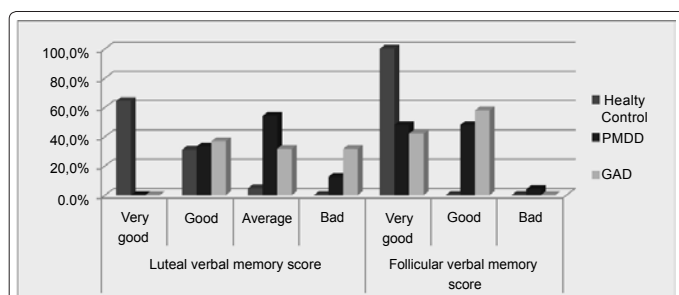


Figure 1: Percent ratios of Wechsler Verbal Memory Test scores of Premenstrual Dysphoric Disorder (PMDD), Generalized Anxiety Disorder (GAD), and healthy control groups by the phases of menstrual cycle.

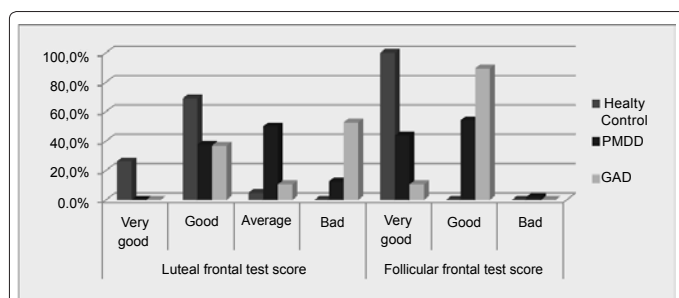


Figure 2: Percent ratios of Frontal Assessment Battery Test scores of Premenstrual Dysphoric Disorder (PMDD), Generalized Anxiety Disorder (GAD), and healthy control groups by the phases of menstrual cycle.

		Healthy Control		PMDD		GAD		Chi-Square	p
		n	%	n	%	n	%		
Luteal frontal test score	Very good	11	26.2%	0	0.0%	0	0.0%	81.45	0.000
	Good	29	69.0%	18	37.5%	14	36.8%		
	Average	2	4.8%	24	50.0%	4	10.5%		
	Bad	0	0.0%	6	12.5%	20	52.6%		
Follicular frontal test score	Very good	42	100%	21	43.8%	4	10.5%	68.20	0.000
	Good	0	0.0%	26	54.2%	34	89.5%		
	Bad	0	0.0%	1	2.1%	0	0.0%		
Luteal and follicular phase difference	z	-5.416		-5.225		-4.650			
	p	0.000		0.000		0.000			

Chi-square/ Wilcoxon test/ 95% confidence interval

Table 3: The distribution of Frontal assessment battery scores of sample groups in terms of menstrual phases. Those with a FAB score of 16-18 are classified as "very good", 13-15 as "good", 10-12 as "average", and 10 < as "bad" ($P < 0.0001$).

neurocognitive abilities from which frontal lobe is responsible may be explained by the theories about cognitive process of anxiety. One of the common features of these theories is mental activity with knowledge of menace [25-27]. Anxiety causes the attention to focus on internal (concern) or external menace to decrease resources of attention necessary to complete a test [27]. Inhibition and verbal fluency measures are the leading ones. Thus, it is an expected result that GAD group shows a worse performance in tasks in which the attention should become faster or change focus. Basso et al. reported that anxiety comorbidity potentially underlies supervisory cognitive functional deficits observed in depression [28]. Clinical depression unaccompanied by age-matched anxiety has not been found to be related to supervisory functional disorders in younger or older adults [29]. Stroop test generally assesses selective attention and inhibitor capacity, i.e. concentration ability. As patients in GAD group exhibit an excessive amount of cognitive overload for the inhibitor skill, it may be concluded that there was no significant differences between groups in terms of stroop test points. In other words, excessive worry serves as a coping strategy. For instance, a study exploring the relationship of symptoms of anxiety and depression with cognitive performance revealed that elderly with a former clinical diagnosis of GAD have a more advanced inhibitory ability [30].

The results of our study shows that women in healthy control group did not experience significant mood disorders, physical symptoms, and irritability, the major finding of PMDD, during luteal phase. There was a significant increase in irritability and dysphoric mood in women with PMDD in late luteal phase compared to their own follicular phase, and GAD and control groups. These findings were consistent with former studies reporting luteal phase dysphoric mood in women with PMDD (7- 10). In this study there were no significant changes in anxiety symptoms by menstrual phases in patients with GAD.

The ratio of change in progesterone during menstrual phases was significantly higher in GAD group than PMDD or healthy control groups. The studies on the effects of progesterone in female body are limited in literature. However, it is acknowledged that progesterone is physiologically important in neurocognitive processes [13]. This finding may be the reason for performance decline in verbal memory and global frontal abilities observed in GAD group in late luteal phase. The ratio of change in estrogen level by menstrual cycle, on the other hand, was significantly higher in both patient groups compared to healthy groups. This result is consistent with the finding of independent effects of fluctuations in estrogen levels on both physiologic and psychological processes during menstrual cycle [7].

There are some limitations in this study. Patients in the GAD group had some level of depressive symptoms given the known comorbidity between these conditions. Also some other factors like sleep quality could affect cognitive performance. These potential confounders make it difficult to interpret whether any observed differences result from the group conditions or unmeasured factors. The other limitation is psychotropic drug use in GAD group. It should be clarified whether more advanced inhibition ability in this patient group is due to such treatment or cognitive education. Elucidation of biologic and genetic moderators and analysis of their relationship would be a giant step in that field. Slight but effective changes in mood, emotion, perception, appetite, and neurocognitive functions produced by the interplay between central nervous system, autonomic nervous system, reproductive system, and immune system has only recently begun to be explained. We think that we may be able to maintain woman's mental health more efficiently for a lifetime as the prevalence of estrogen and

progesterone receptors are more thoroughly defined and their role more clearly explained.

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