Oxidative stress and neurocognitive function in patients with autogenous and reactive type OCD

Otojen ve reaktif tip OKB'de oksidatif stres ve nörokognisyon

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SUMMARY

Objective: The number of studies investigating oxidative stress levels in OCD subtypes is limited. This study aimed to compared total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index values between OCD subtypes and to determine relationship between oxidative stress and neurocognitive function. **Method:** T19 autogenous type OCD, 21 reactive type OCD and 42 healthy controls were taken to this study.All patients were rated using the Yale-Brown Obsessive Compulsive Scale, the Metacognition Questionnaire, the Beck Depression Inventory and Beck Anxiety Inventory, the Wisconsin Card Sorting Test, and the Stroop test. Serum TOS and TAS levels were determined. **Results:** TAS levels were significantly higher in patients with OCD (p=0.018) than in the healthy controls. TAS levels were also significantly higher in patients with RT type OCD than in the healthy controls (p=0.003). In RT OCD, TAS was correlated with the Wisconsin Card Sorting Test – trials to complete the first category (p=0.02) and the Metacognition Questionnaire - need to control thoughts (p=0.02) subscales. **Discussion:** The study findings indicated an overall oxidative imbalance shift toward the antioxidant side in patients with OCD and RT type OCD. This may be a way of coping with the disease. The correlation between TAS and the Wisconsin Card Sorting Test – trials to complete the first category subscale suggests that the change in serum TAS level may be a condition that for overcoming mental inflexibility. These results should be confirmed by prospective studies.

Key Words: Obsessive compulsive disorder, Oxidative stress, cognition, Autogenous obsessions, Reactive obsessions, cognitive dysfunction

ÖZET

Amaç: OKB altiplerinde oksidatif stres düzeylerini araştıran çalışma sayısı sınırlıdır. Bu çalışma total oksidatif stres(TOS), total antioksidan düzeyi (TAS) ve oksidatif stres indeksini Obsesif Kompulsif Bozukluk (OKB) altiplerinde karşılaştırmak ve oksidatif stresle nörobilişsel işlevler arasındaki ilişkiyi tespit etmek amacıyla planlanmıştır. **Yöntem:** Bu çalışmaya19 otojen tip OKB, 21 reaktif tip OKB VE 42 sağlıklı kontrol alınmıştır.Tüm hastalara Yale-Brown Obsesif Kompulsif derecelendirme Ölçeği, Metakognisyon Ölçeği, Beck Depreson Ölçeği ve Beck Anksiyete Ölçeği, Stroop Testi ve Winconsin Kart Eşleme ölçeği uygulanmış ve serum TOS ve TAS düzeylerine bakılmıştır. **Bulgular:** Serum TAS düzeyi OKB hastalarında sağlıklı kontrollere göre anlamlı yüksek tespit edilmiştir(p=0.018). Serum TAS seviyesi Reaktif Tip OKB'de sağlıklı kontrollere göre anlamlı yüksek bulunmuştur(p=0.003). RT OKB'de serum TAS düzeyi Winkonsin Kart Eşleme Testi-ilk kategoriyi tamamlama için deneme sayısı ve Metakognisyon testi-düşünceleri kontrol etme ihtiyacı alt ölçeği ile korele bulunmuştur(sırasıyla p=0.02 p=0.02). **Sonuç:** Bu çalışma OKB hastalarında ve Reaktif Tip tip OKB hastalarında oksidatif stresin antioksidan yöne doğru bir kaymaya yolaçtığını göstermiştir. Bu değişiklik hastalıkla baş etmede kullanılan bir başa çıkma yolu olabilir. TAS ve Winconson Kart Eşleme testi arasındaki korelasyonun tespit edilmiş olması serum TAS düzeyindeki değişimin zihinsel esnekliğe etki edebilen bir durum olabileceğini düşündürtmektedir. Bu çalışmanın sonuçları ileri çalışmalarla doğrulanmalıdır.

Anahtar Sözcükler: Obsesif kompulsif Bozukluk, Oksidatif stres, kognisyon, otojen obsesyon, reaktif obsesyon, bilişsel yetmezlik

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INTRODUCTION

Oxidative stress is a deterioration in the oxidant-antioxidant balance, in which oxidant level increase, leading to increased generation of reactive oxygen radicals disrupting the basic component of the membranes (1). Excessive oxidative stress may damage critical cellular functions, including those in the brain. The effect of oxidative stress in different psychiatric diseases, including obsessive compulsive disorder (OCD), has already been described in the literature, suggesting that oxidative stress also plays a role in pathogenic pathways(2). Oxidative stress resulting from increased free radicals or antioxidant defense mechanisms has also been reported in OCD, and has been associated with various clinical indicators. Maia A et al. reported increase oxidative processes in OCD patients in their meta-analysis, and also pointed out the deficits of stratification based on clinical features (3). Another unclear issue is which clinical features of OCD are associated with oxidative stress and whether oxidative stress is associated with inadequate antioxidant response. OCD has frequently been associated with cognitive dysfunction, including several executive functions, but no OCD-specific neuropsychological profile has to date been established (4). Obsessions can be subtyped with cognitive theory of Lee and Kwon for establishing homogeneity of the disease (4). Obsessions are divided into autogenous and reactive according to Lee and Kwon's cognitive theory. Aggression and religious and sexual obsessions are accepted as autogenous obsession which induces more anxiety with high repetition. On the other side reactive obsessions include contamination, doubt, symmetry, ordering and hoarding lead less discomfort in the individual (5). Inconsistent results concerning cognitive dysfunctions in OCD may be the result of heterogeneity in clinical presentations of the disorder in different studies. Bragdon et al. underscored the importance of taking OCD symptom heterogeneity into consideration in their meta-analysis (6) Levels of oxidative stress parameters in distinct clinical subtypes of OCD and the relationship with cognitive decline have not been previously studied. Although it is known that negative effects of oxidative stress on executive functions occur with age and can also be seen in age-related diseases (7,8), its effect on cognitive functions in OCD has been little studied. The aim of this study to compare total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) values between different types of OCD (autogenous [AT] and reactive [RT]) and healthy controls and to examine the impact of oxidative stress on different clinical OCD subtypes. Furthermore relationship between oxidative stress parameters and neurocognitive functions were studied. In this study, we hypothesized that cognitive impairment would be related to an increased in oxidative stress levels. This hypothesis will illuminate the biological mechanism underlying the classification of AT and RT types of OCD based on cognitive processes. Thus, new treatment strategies with neurobiological bases can be identified in further studies.

METHOD

Survey Design

This study was carried out in a cross-sectional design with patients who applied to Karadeniz Technical University Psychiatry outpatient clinic for 12 months. Nineteen patients with AT and 21 patients with RT type OCD and sex- and age-matched 42 healthy controls were enrolled into the study. Patients were followed-up at the Karadeniz Technical University Medical Faculty Psychiatry Unit outpatient clinic, Turkey. The study was approved by the local ethical committee of the Karadeniz Technical University Faculty of Medicine. All participants gave written informed consent after receiving a full explanation of the study protocol.

Participants

All patients were rated using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Metacognition Questionnaire (MCQ-30), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). OCD patients were divided into 2 subgroups according to the classification created by Lee and Kwon (5). Patients with one or more of aggression, religious or sexual obsessions as primary obsessions were assigned to the AT OCD group. Patients with one or more of contamination, doubt,

symmetry or hoarding as primary obsessions were included in the RT OCD group. Neurocognitive scales including the Wisconsin Card Sorting Test (WCST) and the Stroop Test were administered in the same order to all patients and healthy controls (2). The Y-BOCS consists of a 74-item symptom checklist that control obsessions and compulsions, and 1 section with 10 items that assess severity. The scale has demonstrated good inter-rater reliability, internal consistency, and convergent validity (3). A self-report instrument , BDI was used to measure the severity of depression (4). The Metacognition Questionnaire (MCQ) was originally developed and subjected to psychometric investigation by Cartwright-Hatton and Wells. A short version was subsequently developed in 2004 (5,6). The questionnaire consists of five factors including (1) positive beliefs, (2) cognitive confidence, (3) uncontrollability and danger, (4) cognitive self-consciousness, and (5) the need to control thoughts. Each item on the MCQ-30 is rated on a 4-point Likert scale; scores range from 30 to 120, with higher scores indicating greater pathological metacognitive activity. The psychometric properties of the scale were validated for the Turkish version (7). The WCST is a test that evaluates executive functions. Executive functions that the test evaluates include cognitive flexibility, perseverative tendencies, and ability to shift sets (8). The present study measured WCST total errors, perseverative errors, non-perseverative errors, trials to complete the first category, and numbers of categories completed. The Stroop color–word task, introduced by Stroop in 1935, is used for assessing the interference phenomenon, suggested as executive function including interference resolution and response inhibition (9, 10). TAS is an indicator of the activity of all antioxidant molecules, while TOS is an indicator of all reactive oxygen species. OSI is the ratio of TOS to TAS and an indicator of the degree of oxidative stress (11,12).

Samples were collected separately into vacutainer tubes without anticoagulant. They were then centrifuged at 2000xg for 10 min, and the upper serum parts were collected. The serum samples were transferred to small closed tubes and stored at-80ºC until measurement of oxidative stress parameters. Serum TOS and TAS levels were determined using commercial colorimetric kits (Rel Assay Diagnostics, Gaziantep, Turkey) according to the manufacturer's recommendations. TOS and TAS results were expressed as μmol H2O2 equivalent/L and mmol trolox equivalent/L, respectively. OSI was calculated as the TOS:TAS ratio. Units of TAS expressed as mmol Trolox equivalent/L were converted to μmol Trolox equivalent/L, and OSI was calculated using the formula (13)

OSI=[(TOS, μmol H2O2 equivalent/L) / (TAS, μmol Trolox equivalent/L) x 100]. Exclusion criteria for the study were ECT treatment in the last 6 months, substance-alcohol use, presence of medical disease including neurological diseases, infections, allergopathies, inflammatory disorders, immunological disorders, endocrine and metabolic diseases, obesity or recent weight loss, pregnancy or antibiotic or use.

Data Analysis

The conformity of the data to the normal distribution was made with the Kolmogorov-Smirnov test. Numerical variables were compared using Student's t test for non-normally distributed variables in two independent groups, while the chi-square test was used for categorical variables in independent samples. The significance level was set at two-tailed $p<0.05$. In this study, interval data were expressed as mean ± standard deviation and nominal data were expressed as percentages. Correlation analyses were performed with Pearson test for normally distributed variables and Spearman analysis for non-normally distributed data. The Shapiro–Wilks test was applied to data that did not fit the normal distribution. The source of difference has been determined with Bonferroni analysis. Post-hoc Bonferroni type adjustment was applied in multiple comparisons, with a p value less than 0.016. In order to compare means, analysis of variance (ANOVA) was used for normally distributed data, and Kruskal–Wallis test was used for data that did not show normal distribution.

RESULTS

Nineteen(47.5%) patients with AT OCD, 21 (52.5%) with RT OCD, and 42 healthy controls were included in this study. The mean age of the

Table.1: Sociodemographic and Clinical Variables in the AT OCD, RT OCD and Control Groups

	AT OCD	RT OCD	Control	p
	Mean– SD	Mean– SD		
Age (years)	27.26–12.03	28.52–12.54	27.81 –11.84	0.963
Education (years)	12.84–3.18	12.48–3.93	12.33 –3.57	0.493
Sex	%(n=)	%(n=)		0.361
Female	47.4(n=9)	66.7(14)	59.5(n=25)	
Male	52.6(10)	33.3(n=7)	40.5(n=17)	
Duration of the most recent episode (months)	11.47–15.72	24.19–27.39		0.034*
Duration of the most recent treatment period (months)	10.00–16.38	18.15–16.54		0.036*
BDI	17.26–7.66	12.57–8.63	1.71–2.24	0.000*
BAI	13.68–8.14	9.00–8.81	0.42–1.26	0.000*
YBOCS Total score	32.79–9.36	24.48–923	0.00–0.00	0.008*
MCQ-30 Total	82.26– 14.76	74.76– 12.33	64.43–12.90	0.000*
Need to control thoughts	19.11–3.63	16.38–4.06	12.81– 3.98	0.000*
Cognitive self-consciousness	17.47–2.65	17.43–3.29	13.31– 3.65	0.04*
Negative beliefs about uncontrollability and danger	18.79–3.34	15.95–3.24	12.40– 3.97	0.000*
TAS	2.26–0,41	2.45–0.35	2.14–0,43	0.008*
TOS	5.53–1,42	5.34–1,10	5.43–2,47	0.994
OSI	0.25–0,07	0.22–0,05	0.27–0,16	0.187

OCD: Obsessive compulsive disorder, AT: Autogenous type, RT: Reactive type, BDI: Beck Depression Inventory, BAI: Beck Anxiety, Inventory, YBOCS: Yale-Brown Obsessive Compulsive Scale, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, Mean– SD: Mean plus standard deviation *: p less than 0.05 between the three groups

AT OCD group was 27.26±12.03, sex distribution was 47.4% (9) female and 52.6% (10) male, and mean length of education was 12.84 ±3.18 years. While the mean age of the RT OCD group was 28.52±12.54, it was 27.81±11.84 years in the control group. Sex distribution was 66.7% (n=14) female 33.3% (n=7) male in RT OCD, 40.5% (n=17) male 59.5% (n=25) female in the control group. There was no significant difference was determined between the two groups in terms of age, sex distribution or education levels (p= 0.963, 0.361, and 0.493, respectively). Additionally, 73.7%(n=14) of the AT OCD group and 95.2% (n=20) of the RT OCD group were currently receiving treatment. No significant difference was determined in terms of treatment status (p=0.085). In the AT OCD group, duration of disease was 10.00 ±7.78 years, age at onset was 17.26 ±9.05 years, and duration of the most recent treatment period was 10.00 ±16.38 months. The equivalent values in the RT OCD group were 11.29±10.64 years, 17.24±4.90 years, and 18±16.54 months. No significant difference was observed between the AT and RT OCD groups in terms of duration of disease or age at onset (p=0.893, and 0.390, respectively). The duration of the most recent treatment period was significantly longer in patients with RT OCD (p=0.036). The duration of the most recent episode was 11.47±15.72 months (min: 1 max: 60) in AT OCD, and 24.19±27.39 months (min: 1 max: 120) in RT type OCD. The duration of the most recent episode was significantly longer in the RT OCD group than in the AT OCD group (p=0.034). Sociodemographic and clinical variables in the AT OCD, RT OCD, and control groups are shown in Table 1. Total BDI and BAI scores were higher in AT OCD than in RT OCD (p=0.329), but they are not significant. BDI and BAI scores were significantly higher in AT OCD and RT OCD compared to the healthy controls (p=0.000 for both). Total Y-BOCS scores were significantly higher in AT OCD (32.79±9.36) than in RT OCD (24.48±9.23). Obsession, compulsion, total, insight, general severity, and reliability subscores of Y-BOCS were also significantly higher in AT OCD than in RT OCD (p=0.007, 0.008, 0.008, 0.012, 0.034, and 0.012, respectively). MCQ-30 total, need to control thoughts, and cognitive self-consciousness scores differed significantly between the AT OCD, RT OCD, and healthy control groups (p=0.00, 0.007, and 0.00, respectively). The scores were significantly lower in the healthy controls than in the AT and

Table 2: Neurocognitive Test Scores in the AT and RT OCD Groups

	AT OCD Mean– SD	RT OCD Mean– SD	*p*
WCST		5.70 –2.2	
Perseverative reactions	19.21 –7.09	10.76–5.52	0.000*
Perseverative errors	10.89 –6.51	9.76 –4.13	0.000*
Categories completed	3.05 –0.97	3.19 –1.25	0.001*
Trails to complete the first category	14.21–4.39	15.99–6.49	0.014
Stroop Test			
Total Interference Score	16.10 –8.19	14.90 –7.87	0.006*

OCD: Obsessive compulsive disorder, WCST: Wisconsin Card Sorting Test, Mean– SD: Mean plus standard deviation
*p< 0.05

RT OCD groups. The highest scores were observed in AT OCD, although this was not statistically significant. MCQ-30 negative beliefs about uncontrollability and danger scores were significantly higher in AT OCD than in RT OCD and the healthy controls (p=0.005, and 0.000, respectively). TAS was correlated with the MCQ-30 need to control thoughts subscale in RT OCD (p=0.02). WCST perseverative error and perseverative reaction scores were significantly higher in AT OCD, while numbers of completed categories and trials to complete the first category were higher in RT type OCD. The interference score on the Stroop test was higher in AT type OCD than in RT type OCD (p=0.006). No difference was determined in blood TOS and OSI between the AT OCD, RT OCD and control groups (p= 0.954, and 0337, respectively). However, TAS levels were significantly higher in patients with RT OCD than in AT type OCD and the healthy controls (p=0.008).

Neurocognitive test scores of the AT and RT OCD groups are shown in Table 2. Correlation between TAS values and neurocognitive test scores in patients with AT OCD, RT OCD and the healthy controls are shown in Table 3.

DISCUSSION

OCD is a disease that manifests itself with heterogeneous symptoms with a complex neurobiological basis. Data concerning the role of oxidative stress in the pathophysiology of OCD are limited and inconsistent. While some studies have reported no differences in OXI values in patients with OCD, others have reported oxidative imbalance shifts in favor of either antioxidants or oxidants (21-24) Maia et al. reported a statistically significant increase in oxidant markers due to inadequate buffering by antioxidant mechanisms in patients with OCD. However, sensitivity analyses capable of assessing the impact of patients' clinical or demographic characteristics were not performed in that study. The present study determined an overall oxidative imbalance shift toward the antioxidant side across different clinical presentations including patients with RT type OCD. The demographic and clinical characteristics of the study sample may therefore be a factor involved in the difference observed across the oxidant/antioxidant balance. Patients with AT OCD constituted more severe cases of OCD with lower TAS levels, possibly indicating that a weaker antioxidant mechanism may have aggravated the OCD symptoms. From another point of view, it can be suggested that increased TAS levels in RT-type OCD are a defense mechanism for coping with the disease. MCQ-30 - need to control thoughts subscale score which is accepted as an OCD symptom marker, was found to be lower in RT OCD and positively correlated with serum TAS levels (14-16, 24-26, 31-33). This view is sup-

Table 3: Correlation of TAS and Neurocognitive Test Scores in the AT OCD, RT OCD and Control Groups

	AT OCD TAS		RT OCD TAS		Control TAS	
	p	R	p	r	p	r
WCST						
Perseverative reactions	0.550	-0.146	0.296	-0.239	0.257	0.179
Perseverative errors	0.510	-0.161	0.211	-0.285	0.140	0.232
Categories completed	0.302	0.250	0.909	-0.026	0.236	-0.187
Trials to complete the first category	0.323	0.240	0.020*	0.505	0.706	0.060
Stroop Test						
Total Interference score	0.150	-0.344	0.422	0.185	0.955	-0.009

OCD: Obsessive Compulsive Disorder, WCST: Wisconsin Card Sorting Test, *: p<0.005, r:correlation coefficient

ported by Irak and Tosun, who reported that obsessive compulsive symptoms are a basic metacognitive factor in the need to control thoughts (26). The impact of treatment on antioxidant capacity and TOS in major depressive disorder (MDD) and schizophrenia has been reported previously. Cumurcu et al. also reported lower serum TAS values in MDD patients than in healthy controls, as well as a significant increase in serum TAS following antidepressant therapy (17, 27). In this study, it was shown that serum TAS levels were higher in RT OCD patients with a longer last treatment period than in AT OCD patients with a shorter treatment period. It can be argued that the duration of the treatments applied may increase the antioxidant levels. Lower plasma TAS levels have been reported in treatment-naive schizophrenia patients compared to healthy controls (28). Patients with AT OCD may share a variety of clinical features with schizophrenia, such as thought disorder and schizotypal personality features and abnormal perceptual distortions (30) and may show similar association with oxidative stress due to common neurobiological basis. Since it has been demonstrated clinically and in the field of research that that schizophrenia and OCD exhibit a substantial overlap in terms of structural and functional brain abnormalities and of the pathophysiology underlying these disorders (29). So, the two di-seases may have common points in terms of oxidative stress. An alternative mechanism concerning the variation in oxidative indices may involve other unknown neurobiological mechanisms rather than typical clinical manifestations. The duration or chronicity of the disease may be another factor for changes in oxidative indices. In addition, Selek et al. also attributed the increase in antioxidant levels in OCD patients to the chronicity of the disease or a rebound phenomenon (31). In the present study, the duration of the most recent episode and the most recent treatment period were found higher in RT type OCD. Long-term exposure to disease may have increased the antioxidant mechanisms in RT type OCD, or alternatively the treatment may have activated antioxidant mechanisms.

The methods of analysis employed in the investigation of antioxidant mechanisms may also be a factor in the inconsistent results across the various previous studies Oxidative stress has also been investigated by assessing various biochemical parameters other than TAS, TOS and OSI (23,32), and elevation has been reported in patients with OCD. Serum concentrations of different oxidative components can be measured separately in the laboratory, but the measurement of these molecules is difficult and time-consuming, and involves complicated techniques and high costs. In the present study, TAS, TOS, and OSI values were used to reflect the redox balance between oxidants and antioxidants. In contrast, Behl A et al. investigated oxidative imbalance by measuring malondialdehyde and superoxide dismutase levels, and observed an oxidative imbalance leaning towards the antioxidant side in OCD (23).

Another important finding in this study is a significant difference between the OCD patients and healthy controls in terms of WCST and Stroop interference, but non between the patients with RT OCD and AT OCD. A similar finding was reported in a previous study, which emphasized that a larger sample might yield more substantive results (33). Oxidative stress-related cognitive dysfunctions have been investigated in animal models, and have been shown to result in deleterious consequences for cognition (34). There is also evidence for a therapeutic role of antioxidants in cognitive deficits, although further investigation is still required (35). In clinical trials, biochemical parameters leading to oxidative stress were reported to be associated with neurodegenerative and neuropsychiatric disorders (36,37).Plasma TAS has been linked to various domains of cognitive deficits in drug-naive patients with schizophrenia (28).However, the role of oxidative stress in cognitive dysfunction in OCD was not elaborated. In the present study, TAS values were higher in OCD patients and in RT type OCD, and the level of TAS was correlated with trials to complete the first category in WCST in OCD and RT type OCD patients, assumed to be associated with lower cognitive flexibility. These results may indicate that antioxidant levels rise as cognitive flexibility worsens. This is in contrast to Bradbury's study, which reported neurocognitive deficits in a high beliefs OCD subgroup compared to a low beliefs OCD subgroup (18, 38). This may be because the study sample included different clinical OCD subtypes. In this study, oxidative stress was only correlated with WCST- trials to the

first category in OCD and RT type OCD patients, which may suggest that an antioxidant mechanism operates in order to overcome cognitive inflexibility. The fact that cognition is worse and symptoms are more severe in AT OCD suggests that antioxidant mechanisms are not as effective as in RT type OCD. A direct relationship has been determined between executive function and antioxidant protective factors in first episode psychosis among psychiatric conditions other than OCD (39). In contrast to these positive findings, other studies have reported no significant associations between antioxidant defense markers and Trail Making Test or Stroop Test scores in patients with recurrent depressive disorder (40). Aydemir et al. also observed no correlation between cognitive impairment and oxidative stress in patients with bipolar disorder (41). In our study, TAS was only correlated with WCST - trials to the first category, and not with Stroop interference. The absence of an association between Stroop interference and antioxidant levels may indicate that some cognitive functions are related to oxidative stress, while another parts are not. Another explanation is that the link between oxidative stress and cognitive functions in OCD is evident in diversified clinical subtypes.

CONCLUSION

Our findings revealed an overall oxidative imbalance shift toward the antioxidant side in OCD. This result may develop as a result of a rebound phenomenon or due to the due to chronicity of the disease. The question of whether oxidative stress is the cause or the result of the disease process in OCD remains unclear, and further detailed and extensive studies designed on a longitudinal basis are now needed. Although low mental flexibility has been shown to activate antioxidant mechanisms in patients with RT type OCD, if the temporal relationship between them is clarified, the hypothesis put forward in this study will be strengthened.

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Disclosure Statement

The authors declare no conflict of interest.

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