

Psychiatric analysis of treatment-resistant allergic rhinitis and evaluation of the effects of antidepressant use

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Abstract

Objective: We evaluated the incidence of psychiatric disorders in patients with allergic rhinitis (AR) and assessed the effects of the use of antidepressants on symptoms when they are included in the treatment regimen of patients with AR who are resistant to AR treatment.

Methods: A total of 49 patients who were resistant to the treatment for AR and who did not accept the option of immunotherapy were included in the study. Thirty-eight of the 40 patients were advised to take the antidepressant sertraline; however, only 21 of them agreed to use the medication while 17 of them refused. The 21 patients who agreed to begin the antidepressant were also advised to undergo AR treatment with desloratadine once per day and intranasal mometasone furoate once per day (Group 1). The patients who refused to use the antidepressant were advised to begin the AR treatment (Group 2). Symptom scoring for AR was again performed for all patients 6 weeks after treatment. The Psychological Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI TX I and TX II) were performed on the patients in the company of a psychiatrist.

Results: The post-treatment nasal and non-nasal symptom scores in Group 1 were significantly better than the pretreatment scores for any of the seven symptoms ($p=0.000$). No significant correlation was found between the AR symptom scores and the average SCL-90 general symptom score, the SCL-90 subscale scores, the total BDI scores, and the STAI scores ($p>0.05$).

Conclusion: This study suggests that the use of antidepressants diminishes the allergic symptoms in patients with treatment-resistant AR since psychosomatic factor is of great importance in the patient population of AR.

Keywords: Psychiatric disorders, allergic rhinitis, antidepressant.

Özet: Tedaviye dirençli alerjik rinitin psikiyatrik analizi ve antidepressan kullanımı etkilerinin değerlendirilmesi

Amaç: Bu çalışmada alerjik rinit (AR) hastalarında psikiyatrik bozuklukların insidansı ve AR tedavisine dirençli AR hastalarının tedavi rejimine dahil edildiğinde antidepressanların etkilerini değerlendirmeyi amaçladık.

Yöntem: Çalışmaya AR tedavisine dirençli ve immünoterapi seçeneğini kabul etmeyen toplam 49 hasta alındı. Kırk hastanın 38'ine antidepressan sertralin alması önerildi. Ancak yalnızca 21'i ilacı kullanmayı kabul ederken 17'si reddetti. Antidepressana başlamayı kabul eden 21 hastaya ayrıca günde tek doz desloratadin ve intranasal mometason furoat alması önerildi (Grup 1). Antidepressan kullanmayı reddeden hastalara AR tedavisine başlaması önerildi (Grup 2). Tedaviden 6 hafta sonra hastaların tümünde yeniden AR için semptom skorlaması yapıldı. Bir psikiyatrist nezaretinde hastalara Psikolojik Semptom Kontrol Listesi-90 (The Psychological Symptom Checklist-90; SCL-90), Beck Depresyon Envanteri (Beck Depression Inventory; BDI) ve Anksiyete Durum Envanteri (State-Trait Anxiety Inventory; STAI TX I ve TX II) uygulandı.

Bulgular: Grup 1'de tedavi sonrası nazal ve nazal olmayan semptom skorları yedi semptomun her biri için tedavi öncesi skorlardan anlamlı derecede daha iyiydi ($p=0.000$). AR semptom skorlarıyla ortalama SCL-90 genel semptom skoru, SCL-90 altölçek skorları, total BDI skorları ve STAI skorları arasında anlamlı bir korelasyon bulunmadı ($p>0.05$).

Sonuç: AR popülasyonunda psikosomatik faktör büyük önem taşıdığından bu çalışma antidepressan kullanımının tedaviye dirençli AR'de alerjik semptomları azalttığını akla getirmektedir.

Anahtar sözcükler: Psikiyatrik bozukluklar, alerjik rinit, antidepressan.

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Allergic rhinitis (AR) is a highly prevalent chronic disease which is reported as 15% to 20% in industrial societies, and 42% in children.^[1,2]

The nasal symptoms in patients with AR may cause sleep disorders at night and concentration difficulty during the day. Moreover, the resulting psychosocial symptoms, such as chronic fatigue, loss of appetite, a low degree of success at school, low self-image, unemployment, irritability, and pessimism, coincide with symptoms of depression and anxiety.^[3,4] Despite the fact that AR affects the patient's quality of life in an extremely negative manner and that patients exhibiting severe symptoms regularly consult with specialists, clinicians do not tend to focus on the psychological effects of AR.^[5] Psychosocial causes of allergic responses have long been of interest among physicians dealing with psychosomatics. After the clinical studies, a discussion has started on the role of psychological factors in allergic reactions, and individuals with AR were reported to be more anxious, obsessive, ambitious, and neurotic than were individuals without AR.^[6,7] In subsequent studies, however, depression, hypochondriasis, psychasthenia, and avoidant personality traits were reported to be associated with allergy.^[8,9] The role of psychological disorders, such as anxiety and depression, in patients with AR, is still being discussed. We believe that psychological disorders such as depression and anxiety trigger the allergic process by both affecting the hypothalamic-pituitary-adrenal (HPA) system and enhancing the immune response associated with Th2 cells and that AR, in turn, aggravates these symptoms and psychological disorders, resulting in a vicious circle.^[10-12]

Given such information, some patients with AR state that their symptoms do not improve despite medical treatment. Therefore, we evaluated the incidence of psychiatric disorders in patients with AR and assessed the effects of the use of antidepressants on symptoms when they are included in the treatment regimen of patients with AR who are resistant to allergic rhinitis treatment.

Materials and Methods

This controlled, randomized, single-blind study was approved by the Research Ethics Committee of the Istanbul Faculty of Medicine, Istanbul University (9 December 2011; 2011/1996-864).

Of all patients who visited the Allergy and Immunology Clinic at Şişli Etfal Training and Research Hospital from January 2012 to July 2012, those clinically diagnosed with persistent, perennial AR according to ARIA and who reacted against at least one allergen with a score of 3+ in the skin-

prick test were assessed (positive test correlated with symptoms). Among these patients, 49 who were resistant to the treatment for AR and who did not accept the option of immunotherapy were included in the study. Treatment-resistant patients were defined as those who experienced no symptom relief after at least 1 year of antihistaminic and intranasal steroid treatment.

None of these patients had any systemic diseases or diagnosed psychiatric disorders. The exclusion criteria were negative skin-prick tests, no history of AR treatment, inconsistency of positive test results with the symptoms, patient eligibility for and acceptance of immunotherapy, the presence of nasal pathology other than AR leading to nasal obstruction (e.g., non-allergic rhinitis with or without eosinophils, chronic sinusitis, septal deviation, conchal hypertrophy, and nasal polyposis), the presence of additional systemic disease, a history of antidepressant use, a known history of psychiatric disease, and conditions that did not allow for the use of antidepressant or antihistaminic medications. All patients underwent anterior rhinoscopy to establish nasal patency, and nasal endoscopy to look at possible polyps.

All patients were informed about the study details and signed a voluntary informed consent form. AR symptom scoring was performed on all patients with treatment-resistant AR. A score of 0 to 3 was given for each question (0, no complaint to 3, serious enough to affect daily life). The questions covered seven symptoms (rhinorrhea, nasal itching, nasal obstruction, sneezing, watery eyes, eye burning-itching, and ear or palatal itching); four of these symptoms were specific to nasal problems, and three were non-nasal symptoms. Each patient's symptom triggers, the timing of events that affected daily life and their relationships with the disease, symptom duration, hospitalization frequency, socioeconomic level, educational background, age, and sex were recorded. The Psychological Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI TX I and TX II) were performed on the patients in the company of a psychiatrist.

At least one psychological problem was found in 44 of the 49 patients (89.7%). A psychiatric consultation involving detailed examination and the one-to-one interview was requested from the patients in whom pathology was assessed. Four patients refused to undergo a psychiatric consultation and were excluded from the study. After 40 patients had undergone their interview with the psychiatrist, they were called for a second check-up 6 weeks later.

At the end of the consultation, 38 of the 40 patients (95%) were advised to take the antidepressant sertraline (Lustral®; Pfizer Medications, Istanbul, Turkey); however, only 21 of them agreed to use the medication. The remaining two patients were not considered to be in need of antidepressants and were thus excluded from the study. As a result, the study involved 38 patients (25 female, 13 male; mean age: 33.3±11.3 years). Twenty-one of these patients began the antidepressant, and 17 refused. The 21 patients who agreed to begin the antidepressant were also advised to undergo AR treatment with desloratadine (Deloday® 5-mg tablets; Vitalis Med, Istanbul, Turkey) once per day and intranasal mometasone furoate (Nasonex Aqueous Nasal Spray®; Schering-Plough Med, Istanbul, Turkey) once per day (50-µg to both nasal cavities twice each morning). This population was defined as Group 1 (n=21). The patients who refused to use the antidepressant were advised to begin the AR treatment (desloratadine and intranasal mometasone furoate only); they were fully informed about this treatment, and its regular use was encouraged. This patient population was defined as Group 2 (n=17). Symptom scoring for AR was again performed for all patients 6 weeks after treatment. All patients in both groups were analyzed regarding the symptom scores, psychiatric analysis results, and psychiatric interview records, and the pretreatment and post-treatment AR symptom scores were compared within and between the groups. The two groups were analyzed separately regarding the symptom triggers and the timing of the events that affected daily life and their relationship with the disease.

The descriptive statistics concerned the frequency, correlation, average, and standard deviation values. The distribution of the variables was evaluated using the Kolmogorov–

Table 1. Age and sex data.

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Age (year)		31.5±11.5	35.1±11.0	0.343
		n (%)	n (%)	
Sex	Female	12 (57.1)	13 (76.5)	0.215
	Male	9 (42.9)	4 (23.5)	

*Independent samples t test/chi-square test. SD: standart deviation

Smirnov test. ANOVA, the independent-samples t-test, and the Mann–Whitney U-test were used to analyze the quantitative data. Repeated-measures analysis was performed using the paired-sample t-test and Wilcoxon test. The chi-square test and Fischer's exact test were used to analyze the qualitative data. The SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

No statistically significant differences were seen in age, sex, symptom duration, hospitalization frequency, socio-economic level, or educational status between the two groups ($p>0.05$) (Tables 1 and 2).

Patients in both Groups 1 and 2 who did not benefit from the AR treatment had high values on the SCL-90, indicating the presence of a psychological disorder. The BDI scores indicated moderate depressive symptoms in both groups, whereas the STAI TX I and II scores indicated anxiety disorders in both groups. No significant difference was found between the two groups (Table 3).

The post-treatment nasal and non-nasal symptom scores in Group 1 were significantly better than the pretreatment

Table 2. The distribution of socio-demographic data.

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Duration of symptoms (year)		5.2±3.3	6.9±6.1	0.429
		n (%)	n (%)	
Hospitalization frequency	Rarely (<3 times/year)	8 (38.1)	11 (64.7)	0.103
	Frequently (>3 times/year)	13 (61.9)	6 (35.3)	
Socio-economic level	Low (<1000 TL)	8 (38.1)	5 (29.4)	0.575
	Moderate-high (>1000 TL)	13 (61.9)	12 (70.6)	
Educational status	Primary/High school	15 (71.4)	15 (88.2)	0.257
	University	6 (28.6)	2 (11.8)	

*Independent samples t test/chi-square test. SD: standart deviation, TL: Turkish Lira

Table 3. The evaluation of psychiatric analysis scales in Group 1 and Group 2.

		Group 1 Mean±SD	Group 2 Mean±SD	p*
SCL-90	Somatization	1.7±0.8	1.6±0.9	0.696
	Obsessive-compulsive	1.7±0.6	1.6±0.8	0.674
	Interpersonal sensitivity	1.7±0.7	1.7±0.8	0.799
	Depression	1.7±0.8	1.5±0.9	0.451
	Anxiety	1.4±0.6	1.3±0.9	0.505
	Anger-hostility	1.7±0.8	1.8±0.9	0.792
	Phobic anxiety	0.9±0.8	0.9±1.0	0.939
	Paranoid ideation	1.5±0.7	1.5±0.7	0.998
	Psychoticism	1.2±0.9	1.2±1.0	0.905
	Other scales**	1.6±0.7	1.6±0.8	0.835
	General symptom scores	1.5±0.5	1.5±0.8	0.769
<i>Between 0.5–1.0: moderate psychological problem; ≥1.0: severe psychological problem.</i>				
Beck depression inventory	Total score	21.4±8.5	20.2±6.7	0.636
<i>17–29 points: moderate depressive symptoms; 30–63 points: severe depressive symptoms</i>				
State-trait anxiety inventory	State anxiety (STAI-S) scores	48.1±10.6	46.1±8.7	0.541
	Trait anxiety (STAI-T) scores	50.3±6.4	49.0±6.3	0.526
<i>>40 points: anxiety disorder</i>				

*Independent samples t test/chi-square test. **Other scales: appetite and sleep disorders, guiltiness. SD: standart deviation, SCL: Symptom check-list; STAI: state-trait anxiety inventory (S: state, T: trait).

scores for any of the seven symptoms ($p=0.000$). In Group 2, significant recovery was achieved in all of the non-nasal symptoms. Among the nasal symptoms, however, only rhinorrhea and sneezing exhibited significant recovery over pretreatment levels. Nasal itching and nasal obstruction symptoms did not demonstrate a significant change after the treatment. A significant difference in the post-treatment sneezing and nasal obstruction symptoms occurred between Groups 1 and 2. In contrast, the rates of change in all nasal and non-nasal symptoms before and after treatment were significantly higher in Group 1 (Tables 4 and 5).

The pretreatment total symptom scores were not significantly different between Groups 1 and 2. Post-treatment total symptom scores were significantly better than pretreatment scores in both Groups 1 and 2. The post-treatment total symptom score was significantly lower in Group 1 than in Group 2 ($p<0.001$). Again, the rates of change in the total symptom score before and after treatment were higher in Group 1 ($p<0.001$) (Table 6).

On the correlation between the hospitalization frequency and symptom scores, the total AR symptom scores of patients who were rarely hospitalized were significantly lower than those frequently hospitalized ($p=0.001$). There was no correlation between another socio-demographic data and symptom scores (sex, socio-economical status, and

educational status). No significant correlation was found between the AR symptom scores and the average SCL-90 general symptom score, the SCL-90 subscale scores, the total BDI scores, and the STAI scores ($p>0.05$).

Discussion

Many authors have investigated the relationship between atopic or allergic diseases and psychological disorders such as depression and anxiety, and many have reported that a psychoneuroimmunologic mechanism might play a role in the pathophysiology of AR.^[13–16] Psychological stress, particularly in obsessive people, may alter the release of mediators by affecting the IgE-allergen cross-linking on the mast cell surface and create allergic symptoms secondary to mast cell activation regulated by the central nervous system through the peripheral nerves.^[17–19] The limbic system may also be associated with allergic reactions; during allergic reactions, psychological changes occur in the central nervous system due to mediators such as serotonin, which has neurotransmitter functions, and vasoactive intestinal peptide.^[20] Some researchers advocate that depression directly affects the development of atopic diseases. Depression affects cortisol release and the function of the HPA cycle, which may contribute to the disorders seen during the development of an allergic immune response.^[21,22]

Table 4. Allergic rhinitis symptom scoring (nasal symptoms).

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Rhinorrhea	Pre-treatment	2.2±0.8	2.2±0.9	0.992
	Post-treatment	1.1±0.8	1.5±0.7	0.083
	Difference (%)	49.2±35.1	22.5±54.0	0.024
	P	0.000	0.013	
Nasal itching	Pre-treatment	2.2±0.7	1.9±0.7	0.103
	Post-treatment	1.2±0.8	1.6±0.7	0.115
	Difference (%)	50.0±33.7	4.9±58.0	0.005
	P	0.000	0.172	
Sneezing	Pre-treatment	2.8±0.4	2.6±0.6	0.329
	Post-treatment	1.1±0.7	1.6±0.7	0.038
	Difference (%)	57.1±31.9	35.3±26.9	0.031
	P	0.000	0.000	
Nasal obstruction	Pre-treatment	2.2±0.7	2.4±0.9	0.555
	Post-treatment	1.2±0.8	2.0±0.9	0.007
	Difference (%)	40.5±48.8	12.7±41.5	0.015
	P	0.000	0.111	
Nasal symptoms total scores	Pre-treatment	9.8±1.8	9.2±1.8	0.321
	Post-treatment	4.7±2.2	6.8±2.0	0.004
	Difference (%)	50.4±27.0	23.1±25.6	0.003
	P	0.000	0.001	

*Independent samples t test/ Paired samples t test. SD: standard deviation

Patients who experience increases in their allergic symptoms and restrictions in their daily activities secondary to the above-described mechanisms experience far more psychological stress in coping with this chronic dis-

ease and complain more about allergic symptoms as a result of the stress experienced. Thus, a vicious circle develops. Either the allergic symptoms must be controlled, or the psychological stress must be suppressed to

Table 5. Allergic rhinitis symptom scoring (Non-nasal symptoms).

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Eye burning-itching	Pre-treatment	2.1±0.8	2.4±0.7	0.293
	Post-treatment	0.8±0.8	1.7±0.7	0.001
	Difference (%)	63.5±38.6	22.5±38.6	0.002
	P	0.000	0.002	
Watery eyes	Pre-treatment	2.1±0.7	2.4±0.6	0.322
	Post-treatment	1.0±0.7	1.8±1.0	0.005
	Difference (%)	54.0±36.1	22.6±33.4	0.009
	P	0.000	0.021	
Ear/Palatal itching	Pre-treatment	2.6±0.7	2.5±0.8	0.591
	Post-treatment	1.2±0.9	1.7±0.8	0.101
	Difference (%)	57.2±33.7	25.4±46.8	0.020
	P	0.000	0.007	
Non nasal symptoms total scores	Pre-treatment	6.9±1.3	7.2±1.4	0.464
	Post-treatment	3.0±2.0	5.2±1.6	0.000
	Difference (%)	57.2±27.7	26.8±16.9	0.000
	P	0.000	0.000	

*Independent samples t test/ Paired samples t test/ Mann-Whitney U test/ Wilcoxon test. SD: standard deviation

Table 6. Allergic rhinitis symptom scoring (nasal and non-nasal symptoms total scores)

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Total symptom scores	Pre-treatment	16.6±2.4	16.4±2.8	0.753
	Post-treatment	7.6±3.7	12.1±2.7	0.000
	Difference (%)	53.2±23.7	25.2±15.8	0.000
	P	0.000	0.002	

*Independent samples t test/ Paired samples t test. SD: standard deviation

break this vicious circle. In the present study, we evaluated whether antidepressants administered to suppress the stress in patients with treatment-resistant allergic symptoms could break this vicious circle or not. Marshall et al. determined that cognitive impairment, mental fatigue, mood changes, and psychological states similar to depression were present when seasonal AR symptoms increased.^[23,24] Tonelli et al. performed a multidisciplinary study involving the fields of molecular biology, psychoneuroimmunology, and pharmacogenetics to elucidate the relationship between AR and psychological disorders.^[25] They advocated that the allergic condition could directly affect the biochemical response in the central nervous system, giving rise to psychological disorders. Moreover, Kiecolt-Glaser et al. demonstrated that stress not only altered allergic symptoms but also changed the laboratory parameters.^[26] Cuffel et al. evaluated more than 600,000 individuals. Depression was present in 85,298 patients with AR and it was 1.7 times more likely to develop in those with than without AR; moreover, anxiety was 1.41 times more likely to develop in those with than without AR.^[27] In a study by Patten and Williams, depression, panic disorder, and social phobia were found to be more prevalent in 12,171 allergic patients than in nonallergic patients.^[28] Similar studies have also shown a relationship between anxiety/depression and allergic diseases.^[29-34] In our study, at least one psychological problem was found in 89.7% of the patients with treatment-resistant AR.

In this study, the SCL-90 was administered as a screening test; its reliability, validity, and effectiveness have been demonstrated previously.^[15,33,35] Bavbek et al. found significant differences in all subscales of the SCL-90, including somatization, depression, and average general symptom scores, between patients with and without allergy.^[33] Lv et al. reported higher SCL-90 scores for somatization, depression, anxiety, anger-hostility, and psychosis in patients with than without seasonal AR. In our study, high scores consistent with those reported in the literature were

observed for all subscales of the SCL-90 and the average general symptoms.^[15]

Comparison of anxiety scores among allergic patients has revealed high State Anxiety Scores (STAI-S) in patients with asthma, AR, and sinusitis and high Trait Anxiety Scores (STAI-T) in patients with asthma and nasal polyposis.^[36] Stauder and Kovacs evaluated 646 allergic patients and found an average STAI-S score of 40.6 and average STAI-T score of 42.9; these high scores were found to be associated with anxiety.^[37] The average STAI-S and STAI-T scores in the two groups in our study were 47.1 and 49.7, respectively. These anxiety scores in patients with AR are higher than those reported previously, supporting the notion of a relationship between AR and anxiety.

BDI is commonly used to measure and assess depressive symptoms with high validity and reliability. Huurre et al. found that the total BDI score was high in allergic patients and identified a relationship between AR and depression.^[32] Bell et al. confirmed a history of allergies in 71% of patients diagnosed with depression.^[38] In our study, the average BDI total score among all patients in both groups was 20.8, indicating the presence of moderate depressive symptoms. This finding suggests that depressive symptoms are present in many patients with treatment-resistant AR. The symptom score for AR is a reliable scale frequently utilized to establish a diagnosis of AR based on the history of the patient.^[15,39,40] Lv et al. suggested that nasal obstruction is associated with obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, and psychosis and that nasal itching is associated with somatization, depression, and anxiety. They also argued that controlling the symptoms of nasal obstruction and nasal itching may contribute to psychological improvement.^[15]

In this study, we saw improvements in all nasal and non-nasal symptoms and the total symptom score after antidepressant and AR treatment in Group 1. However, Group 2 undertook AR treatment only, and improvements were

present only in rhinorrhea and sneezing. In contrast, we noted improvement in all non-nasal symptoms. These outcomes may indicate that when psychiatric improvement occurs, the symptoms of nasal itching and obstruction also regress, but that when psychological stress continues, no changes occur in these symptoms. In other words, despite the fact that we observed no correlation between the AR symptom scores and the psychiatric scores in our study, the severity of nasal itching and nasal obstruction may be affected by psychological improvements. In this study, we found a positive relationship between hospitalization frequency and the total symptom score. This suggests that patients with severe AR symptoms desire to alleviate the symptoms or the disease itself and thus visit hospitals more frequently. However, this increases the costs associated with AR.

In a survey, Özmen et al.^[7] assessed 32 patients with AR who were considered to have a possible psychiatric disorder and 32.9% of the patients stated that they had survived a major event in their lives that had upset them immediately before their allergic symptoms developed. In 44.4% of the patients, the allergic symptoms developed after the psychiatric symptoms had started, while the allergic symptoms were extant in 37.3% of them before the onset of the psychiatric disorder. In our study, 47.3% of the patients stated that their allergic symptoms emerged in the wake of a major event in their lives, such as dismissal from work, the death of a family member, marriage, divorce, pregnancy, or a traffic accident. These findings support the theory that individuals with psychiatric disorders have increased sensitivity to allergens.

As a result, patients must be approached with biopsychosocial integrity. This study suggests that psychiatric disorders may be present in patients with treatment-resistant AR and that the combination of AR treatment and antidepressants may improve both the AR and psychological symptoms. Breaking this vicious circle will reduce the frequency of affected patients to visit hospitals, enhance the response to medical treatment, and decrease the total cost associated with AR. The weaknesses of this study were the absence of a healthy control group, a control group suffering from nonallergic chronic rhinitis and lack of double-blindness.

Conclusion

This study suggests that the use of antidepressants diminishes the allergic symptoms in patients with treatment-resistant AR since psychosomatic factor is of great importance in the patient population of AR. However, additional

placebo-controlled and double-blind studies are required to determine the role of antidepressants among the various AR treatment options.

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