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Single-Nucleotide Polymorphisms of *TNFA* and *IL1* in Allergic Rhinitis

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Abstract

Background: Allergic rhinitis is a complex polygenic disorder of the upper respiratory tract. Given that proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL) 1 seem to play a role in the development of allergic rhinitis, we evaluated the associations between various single-nucleotide polymorphisms (SNPs) of the *TNF* and *IL1* genes in a case-control study.
Methods: The study population comprised 98 patients with allergic rhinitis. Genotyping was performed using polymerase chain reaction with sequence-specific primers for 2 *TNFA* promoter variants (rs1800629 and rs361525), 1 variant in the promoter region of *IL1A* (*rs1800587*), 2 SNPs in the *IL1B* gene (rs16944 and rs1143634), 1 variant in the *IL1* receptor (rs2234650), and 1 in *IL1RA* (rs315952).
Results: Patients who were homozygous for the T allele of rs16944 in *IL1B* had an 8.1-fold greater risk of allergic rhinitis than those with the C allele. In *TNFA*, a significant relationship was also detected between rs1800629 and rs361525 and allergic rhinitis. Except for rs1800587 in *IL1A* and rs315952 in *IL1RA*, significant differences were found between the patient and control groups for all other SNPs.
Conclusions: We found that allelic variants in the *TNFA* and *IL1* genes were not only associated with the risk of developing allergic rhinitis, but also affected disease course and severity.

Key words: Allergic rhinitis. Genetic susceptibility. Single-nucleotide polymorphism. Proinflammatory cytokines. Tumor necrosis factor. Interleukin 1 family.

Resumen

Antecedentes: La rinitis alérgica es una alteración poligénica compleja de las vías respiratorias. El TNF y la familia de la IL-1, como citoquinas proinflamatorias, parecen jugar un papel en el desarrollo de la rinitis alérgica. En este estudio de casos y controles, se evalúan las posibles asociaciones de diferentes polimorfismos de nucleótidos simples (SNPs) de los genes que regulan TNF-α e IL1.
Métodos: Se estudiaron 19 pacientes con rinitis alérgica, los cuales fueron genotipados mediante PCR para primers especie-específicos, para dos variantes del promotor del TNF-α (rs1800629 y rs361525), uno en el receptor de IL1 (rs2234650), dos SNPs en el gen de IL1ß (rs16944 y rs1143634), uno en el receptor de IL1 receptor (rs2234650) y IL1RA (rs315952).
Resultados: En cuanto a los resultados obtenidos, los pacientes homicigotos para el alelo T de rs16944 en IL1ß mostraron un riesgo 8.1 veces mayor de tener rinitis alérgica que los que presentaban el alelo C.
Con respecto al TNF-α, se observó una relación significativa entre los dos SNPs rs1800629 y rs361525 con la presentación de una rinitis alérgica. Excepto rs1800587, en IL1α, y rs315952 en IL1RA, encuentran una diferencia significativa entre el grupo control y el de pacientes para el resto de los SNPs. Algunos SNPs se asociaron con el curso y con la gravedad de la enfermedad.
Conclusiones: En conclusión, encontramos variantes genéticas de TNF-α y IL1 que se asocian con el riesgo de desarrollar una rinitis alérgica, y que tambien afectan al curso y gravedad de la enfermedad.

Palabras clave: Rinitis alérgica. Susceptibilidad genética. Polimorfismos de nucleótidos simples. Citoquinas proinflamatorias. Factor de necrosis tumoral. Familia de la Interleucina 1.

Introduction

Allergic rhinitis is an inflammatory disorder of the upper respiratory tract characterized by clinical symptoms such as sneezing, nasal congestion, nasal pruritus, rhinorrhea, and obstruction of the nasal passages. The disease also has a systemic component that affects peripheral blood, bone marrow, and the lungs [1,2]. It is the most common allergic disease, with an incidence of 10% to 30% in adults and 10% to 46% in children, and its prevalence has been increasing in recent decades, especially in the industrialized world [3]. This polygenic disease is the result of a complex interplay between multiple genetic and environmental factors that significantly impairs patients' quality of life and causes very unpleasant symptoms [3]. In addition, allergic rhinitis is associated with other conditions, such as conjunctivitis and asthma [4].

Despite being the subject of extensive research, the pathogenesis of allergic rhinitis remains poorly understood. The most relevant factors involved in allergic rhinitis are the imbalance between the type 1 and type 2 helper T-cell (T_H) immune responses, selective eosinophil accumulation in the nasal mucosa, allergen-specific immunoglobulin (Ig) production, and interaction between allergens and IgE in the cells of the upper airway [1,5]. The effects of genetic factors on the development of allergic rhinitis are well documented, and several susceptibility loci that could play a role in pathogenesis have been identified [6]. These genetic factors affect not only the development of the disease, but also its severity and treatment [1].

Proinflammatory cytokines, such as those belonging to the tumor necrosis factor (TNF) α and interleukin (IL) 1 families are thought to play a major role in the development of chronic inflammatory conditions [7-10]. TNF-α is a proinflammatory cytokine produced by macrophages, eosinophils, epithelial cells, and mast cells in the bronchi [11]. It is responsible for smooth muscle activation and inducing late-phase plasma exudation, which is associated with increased nasal mucosal output of granulocyte mediators [12]. TNF-α is involved in the production of antigen-specific IgE and of the adhesion molecules responsible for attraction of eosinophils to allergic inflammatory sites [13]. All of the genes in the *IL1* family, including *IL1A*, *IL1B*, their receptors, and the IL1 receptor antagonist (IL-1Ra) are clustered on chromosome 2 (q14-q21) [14]. Haagerup et al [15] showed a linkage between allergic rhinitis and the *IL1* family. The proinflammatory activities of the *IL1* family include a wide variety of effects on immunity, such as increased histamine release from basophils, activation of T cells, and enhanced expression of adhesion molecules and other proinflammatory cytokines, either directly or through a histamine effect [16]. IL-1Rα is an anti-inflammatory cytokine with no agonist activity, unlike IL-1α and IL-1β. It modulates the natural course of inflammation by inhibiting the potentially destructive effects of *IL1* [16]. Several single-nucleotide polymorphisms (SNPs) have been identified in the *IL1* family, and these may affect gene expression. The SNPs are associated with several immune-mediated diseases such as asthma [9]. Genetic control of the agonist-antagonist balance of the IL-1 family could depend on genetic variants affecting the expression of these molecules. In this study, we aimed to investigate the effect of SNPs in the TNF-α and IL-1 families on a group of patients with allergic rhinitis.

Patients and Methods

Study Population

We enrolled 98 patients with allergic rhinitis who were referred to the Children's Medical Center, the Pediatrics Center of Excellence in Tehran, Iran. Randomization was stratified according to gender, severity, and intermittency of disease. All of the patients were diagnosed according to the modified allergic rhinitis criteria in the Allergic Rhinitis and its Impact on Asthma study [17,18]. Demographic and clinical data were collected by interviewing patients and reviewing their clinical history, which was also used to classify disease severity. Total serum IgE concentration was measured using enzyme-linked immunosorbent assay (ELISA). All patients underwent skin prick tests with cockroach, tree pollen, grass pollen, weeds, mold, dust mite, and animal dander. The results were evaluated according to the criteria of the European Academy of Allergy and Clinical Immunology [19]. The control group comprised 140 healthy volunteers with no history of allergic rhinitis and the same ethnicity as the patients and was recruited to determine the frequency of background population alleles. All controls were asymptomatic. The local ethics committee approved the study, and all the participants gave their written informed consent before sampling.

SNP Genotyping

We collected 5 mL of peripheral blood from all the participants in 5% EDTA tubes. Genomic DNA was extracted using a modified salting out method. We applied polymerase chain reaction (PCR) specific-sequence primers (SSP) under identical amplification and detection conditions to determine the allelic frequencies for 2 *TNFA* promoter variants (G/A at –308 [rs1800629] and G/A at –238 [rs361525]), 1 in the promoter region of *IL1A* (C/T at –889, rs1800587), 1 in the promoter region of *IL1B* (C/T at –511, rs16944), 1 in the *IL1B* gene (T/C at +3954, rs1143634), 1 in the *IL1* receptor (C/T pst1 1970, rs2234650), and 1 in *IL1RA* (T/C mspa1 1100, rs315952). The Heidelberg cytokine gene polymorphism SSP kit (Heidelberg University, Heidelberg, Germany) was used for this purpose. PCR was performed using a thermal cycler (Flexigene, Techne) with a final volume of 10 μL containing 6.3 μL of water, 1 μL of genomic DNA (50 ng), 0.5 μL of Taq DNA polymerase (0.5 IU), 2.2 μL of Master Mix, and each primer. We included a part of the β-globin gene as a positive control in each of the primer mixes.

Amplification was performed using the Thermal Cycler (Techne Flexigene, Cambridge, UK) under the following conditions: initial denaturation at 94°C for 2 minutes; denaturation at 94°C for 10 seconds; annealing with extension at 65°C for 1 minute (10 cycles); denaturation at 94°C for 10 seconds; annealing at 61°C at 50 seconds; and extension at 72°C for 30 seconds (20 cycles). PCR products were visualized using 2% agarose gel electrophoresis and a UV transilluminator.

Statistical Analysis

The statistical analyses were performed using SPSS, version 18 (SPSS Inc). A *P* value of <.05 was considered statistically significant. Allelic associations in patients and controls were analyzed using the χ^2 test and Fisher exact test. Odds ratios (OR) and 95%CIs for the effect of all SNPs on the risk of allergic rhinitis were estimated. A 1-way analysis of variance was used to find associations between IgE levels, eosinophil counts, eosinophil percentages, and each allele.

Results

Patient Characteristics

The characteristics of the patients are presented in Table 1. The mean (SD) age of the patient group at the time of the study was 12.95 (8.87) years. Most of the patients were allergic to tree pollen, grass pollen, cockroach, and dust mite. IgE levels, eosinophil counts, and eosinophil percentages were significantly higher in patients with severe allergic rhinitis than in patients with a moderate or milder phenotype (*P*<.05).

Table 1. Clinical Characteristics of Patients With Allergic Rhinitis

Characteristics	Results
Age, mean (SD), y	12.95 (8.87)
Male/female, No.	48/50
Classification, No.	
Intermittent	47
Persistent	51
Severity, No.	
Mild	48
Moderate	23
Severe	27
Serum IgE levels, mean (SD)	135.15 (152.81)
Eosinophil count, mean (SD)	418.15 (314.12)
Eosinophil percent, mean (SD)	4.38 (2.95)
Allergic conjunctivitis, No. (%)	54 (55.1)
Family history of AR, No. (%)	50 (51)
Allergen category, No. (%)	
Cockroach	18 (18.4)
Tree pollen	33 (33.7)
Grass pollen	16 (16.3)
Weed	3 (3.1)
Mold	9 (9.2)
Dust mite	31 (31.6)
Animal dander	4 (4.1)

Abbreviation: AR, allergic rhinitis.

Table 2. Allele and Genotype Frequencies of Patients and Controls

Gene	SNP	Genotype	Controls (n=140) No. (%)	Patients (n=98) No. (%)	Odds Ratio (95%CI)	*P* Value
IL1A	rs1800587	C	186 (68.4)	136 (69.39)	1.05 (0.69-1.59)	.896
		T	86 (31.6)	60 (30.61)	0.95 (0.63-1.45)	.896
		CC	62 (45.6)	48 (49)	1.15 (0.66-1.99)	.703
		TC	62 (45.6)	39 (39.8)	0.79 (0.45-1.38)	.453
		TT	12 (8.8)	11 (11.2)	1.31 (0.51-3.35)	.699
IL1B	rs16944	C	154 (55.4)	106 (54.64)	0.97 (0.66-1.43)	.945
		T	124 (44.6)	88 (45.36)	1.03 (0.70-1.52)	.945
		CC	36 (25.8)	25 (25.8)	0.99 (0.53-1.87)	.897
		TC	82 (59)	15 (15.5)	0.13 (0.06-0.25)	.000
		TT	21 (15.2)	57 (58.8)	8.01 (4.15-15.58)	.000
	rs1143634	C	198 (70.7)	92 (63.89)	0.73 (0.47-1.15)	.186
		T	82 (29.3)	52 (36.11)	1.36 (0.87-2.14)	.186
		CC	70 (50)	38 (52.8)	1.12 (0.61-2.05)	.811
		TC	58 (41.4)	16 (22.2)	0.4 (0.2-0.81)	.008
		TT	12 (8.6)	18 (25)	3.56 (1.5-8.5)	.002
IL1R	rs2234650	C	174 (62.1)	37 (19.89)	0.15 (0.1-0.24)	.000
		T	106 (44.2)	149 (80.11)	6.61 (4.19-10.45)	.000
		CC	54 (38.6)	45 (49.5)	1.56 (0.88-2.75)	.134
		TC	66 (47.1)	44 (48.4)	1.05 (0.6-1.84)	.964
		TT	20 (14.3)	2 (2.2)	0.13 (0.02-0.62)	.004
IL1RA	rs315952	C	64 (22.9)	37 (19.89)	0.84 (0.52-1.35)	.518
		T	216 (77.1)	149 (80.11)	1.19 (0.74-1.93)	.518
		CC	4 (2.9)	4 (4.3)	1.53 (0.31-7.49)	.716
		CT	56 (40)	29 (31.2)	0.68 (0.38-1.23)	.218
		TT	80 (57.1)	60 (64.5)	1.36 (0.77-2.43)	.322
TNFA	rs1800629	A	39 (14.2)	42 (21.43)	1.64 (0.99-2.73)	.055
		G	235 (85.8)	154 (78.57)	0.61 (0.37-1.01)	.055
		AA	0 (0)	4 (4.1)	–	.029
		AG	39 (28.5)	34 (34.7)	1.33 (0.74	.382
		GG	98 (71.5	60 (61.2)	0.63 (0.35-1.13)	.128
	rs361525	A	59 (21.5)	22 (11.22)	0.46 (0.26-0.8)	.005
		G	215 (78.5)	174 (88.78)	2.17 (1.24-3.82)	.005
		AA	1 (0.7)	0 (0)	–	–
		AG	57 (41.6)	22 (22.45)	0.41 (0.22-0.76)	.003
		GG	79 (57.7)	76 (77.55)	2.54 (1.36-4.74)	.002

Abbreviations: CVID, common variable immunodeficiency; Ig, immunoglobulin; IVIG, intravenous immunoglobulin.

Table 3. Associations Between SNP Genotypes and Specific Clinical Findings in Subgroups of Patients With Allergic Rhinitis

Subgroups	SNP	Genotype	Immunoglobulin E Levels, IU/mL	Eosinophil Count	Eosinophil Percentage
Female patients	rs361525 in *TNFA*	GG AG	154.22 63.85	– –	– –
Patients with conjunctivitis	rs361525 in *TNFA*	GG AG	183 64.3	– –	– –
	rs315952 in *IL1RA*	CC TC TT	– – –	723 348 518	8 3.7 5.5
Patients with a family history of allergic rhinitis	rs361525 in *TNFA*	GG AG	205.3 50.6	– –	– –
Patients with sensitivity to cockroach	rs1800629 in *TNFA*	GG AG	154.3 338.6	– –	– –

Frequencies of SNPs

The frequencies of all SNPs and genotypes were compared between the patient and control groups (Table 2). No significant differences were detected between the controls and the patients for rs1800587 in *IL1A* and rs315952 in *IL1RA*. Patients homozygous for the T allele of rs16944 in *IL1B* had an 8.1-fold (95%CI, 4.15-15.58) greater risk of allergic rhinitis than those with the C allele. In addition, an association was found between susceptibility to allergic rhinitis and rs1143634 in *IL1B*, which showed a 3.56-fold (95%CI, 1.5-8.5) increase in the risk of allergic rhinitis in patients who were homozygous for the T allele. In *TNFA*, there was also a significant relationship between 2 SNPs (rs1800629 and rs361525) and allergic rhinitis.

Frequency of Haplotypes

Comparison of the haplotypes of rs1800629 and rs361525 showed that the A/G haplotype was significantly more frequent in the patient group (29.6% vs 14.2%, respectively, $P<.001$; OR, 2.53; 95%CI, 1.56-4.11), whereas the G/A haplotype was found in 2.1% of patients and 21.5% of controls ($P<.001$; OR, 0.12; 95%CI, 0.04-0.28). No significant differences in G/G haplotype were detected between the 2 groups ($P=.547$).

Clinical Associations

No significant relationship was observed between serum IgE levels, eosinophil count, and the percentage of alleles in patients with allergic rhinitis. However, a significant relationship was found between serum IgE levels and rs361525 in *TNFA* in female patients (Table 3). The patient with the AG genotype had lower IgE levels ($P<.05$).

Patients with the CT or TT genotype in rs1800587 in *IL1A* were less likely to be sensitive to dust mite (OR, 0.32; $P<.05$). Furthermore, patients with the TC or TT alleles in rs16944 in *IL1B* were more likely to be sensitive to grass pollen (OR, 6.3; $P<.05$). Patients with 1 C allele in rs315952 in *IL1RA* were less likely to be sensitive to cockroach allergens (OR, 0.2; $P<.05$). We found that genotypes were not only associated with the nature of sensitivity, but were also a determinant of disease severity. Patients with the T allele in rs2234650 in *IL1R* were more likely to have moderate or severe disease (OR, 2.8; $P<.05$). Another SNP with a protective effect on developing

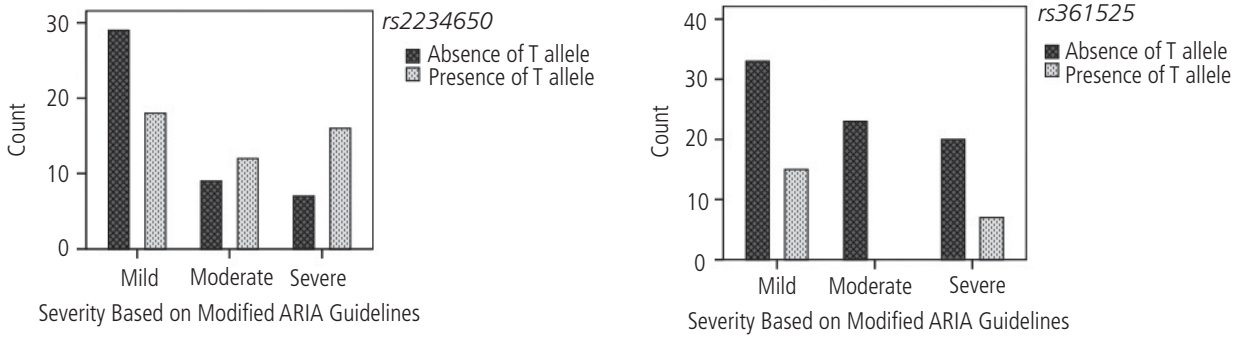

Figure. Association between disease severity and genotypes of rs2234650 and rs361525. ARIA indicates Allergic Rhinitis and its Impact on Asthma.

a severe type of allergic rhinitis was the AG or AA genotype in rs361525 in *TNFA* (OR, 0.4; *P*<.05) (Figure). Patients with 1 C allele in rs315952 in *IL1RA* were less likely to develop persistent disease (OR, 0.3; *P*<.05).

Discussion

We analyzed the role of 7 potentially functional SNPs in 5 genes in susceptibility to allergic rhinitis.

We found a significant relationship between 2 SNPs in the promoter region of *TNFA*. Allergic rhinitis is associated with increased tissue expression of *TNFA* messenger RNA [11]. The SNP rs1800629 in the promoter region of *TNFA* enhances the binding affinity of nuclear factors to the *TNFA* promoter and, subsequently, transcription of TNF-α in stimulated human white blood cells [20], although this effect has not been confirmed in vivo [21]. A systematic review of studies analyzing the association between the *TNFA* –308 promoter polymorphism and asthma showed a clear association between this SNP and overall susceptibility to asthma [22]. The SNP is also associated with atopy [23] and bronchial hyperreactivity [24]. Our study showed that the AA genotype in rs1800629 was significantly more frequent in allergic patients than in controls. TNF-α, which exerts pleiotropic effects, may play different roles in the pathogenesis of allergic diseases, according to the local microenvironment and stimuli and genetic backgrounds. In a subgroup of patients who were sensitive to cockroach, the AG genotype was associated with higher levels of IgE. High levels of cockroach allergens in inner-city housing are a major risk factor for symptoms in sensitized individuals [25]. A gene array analysis showed that more than 50 genes are uniquely expressed in cockroach-treated cells [25]. Proteases in cockroach extracts can induce both the innate and adaptive immune responses, leading to the release of TNF-α through protease-activated receptors (PAR), which are a family of proteolytically activated G-coupled receptors [25], and to allergen sensitization and specific IgE production [26]. Therefore, increased production of TNF-α can increase production of IgE through the PAR pathway. This explanation can be applied to patients who are sensitive to house dust mite, which is also an allergen with proteinase activity. We found a similar—albeit weak—association between IgE levels and this SNP in patients who were sensitive to house dust mite. However, GG is usually considered a low-producing *TNFA* genotype, whereas AG is a high-producing genotype. Considering that the frequency of the GG genotype was significantly increased in allergic patients and the AG genotype was significantly decreased in patients with allergic rhinitis, decreased TNF-α levels could be suspected in allergic patients.

Surprisingly, we found the frequency of the AG genotype in rs361525 in *TNFA* to be significantly lower in patients with allergic rhinitis than in controls. Moreover, it had a protective effect against developing moderate or severe disease. This finding is contradictory to previous results for patients with asthma or nasal polyposis [9,10]. This promoter variant increases the transcriptional activity of *TNFA* [20]. In some subgroups, such as female patients, this genotype was associated with lower IgE levels. Gender and sex hormones are known to influence immunity in a variety of ways, and defense mechanisms against infectious agents differ between men and women [27]. The function of a given allele may be sex-dependent and can therefore give rise to different allelic associations [28].

The *IL1* family plays an important role in the pathogenesis of allergic rhinitis, for example, in allergen-specific T_H2 cell activation [29]. In vivo studies revealed that IL1-Ra exerts a protective effect against allergic rhinitis by reducing levels of histamine and IgE [16]. Levels of IL-1, especially IL-1β, in nasal secretions increase after antigen challenge in patients with allergic rhinitis; however, levels of IL-1Rα decrease in nasal secretions, thus leading to an imbalance in IL-1/IL-1Rα and dysfunction of anti-inflammatory capacity [29].

The SNP rs1800587 in the promoter region of *IL1A* has various effects on serum levels of both IL-1α and IL-1β. Interestingly, healthy individuals who were homozygous for this SNP had higher serum levels of IL-1β. This effect was influenced by the presence of rs16944 in *IL1B* [30]. An in vivo study showed enhancing effect of this SNP on IL-1α and IL-1β protein levels [31].

Our study demonstrated a protective effect of TC for both SNPs in *IL1A* and an increase in the risk of allergic rhinitis in the presence of the TT genotype for these SNPs. This result is inconsistent with the findings of a previous study on allergic rhinitis [29]. However, a study on asthmatic patients revealed the same protective effect of the TC genotype in patients carrying rs16944 [9]. The effect of rs16944 on gene transcription is dependent on the alleles of the 3 other SNPs (–3737, –1464, –31) that were present in the promoter region [32].

In vitro studies have shown that rs1143634 in exon 5 of *IL1B* causes increased secretion of IL-1β [33], although the exact mechanism of this synonymous SNP is not clear. It is speculated that this genotype may lead to upregulation of IL-1β [34] or to a decreased turnover rate and change in alternative splicing activity. rs1143627, another SNP of *IL1B* that is known to alter the transcription of *IL1B*, is in strong linkage disequilibrium with rs1143634 [35].

Homozygosity for rs2234650 in *IL1R* had a protective effect against allergic rhinitis, and the T allele was significantly underrepresented in the patient group. The same negative association was observed in asthmatic patients [9]. Surprisingly, this SNP was significantly associated with moderate or severe disease in patients. No significant relationship was observed between rs315952 in *IL1RA* and susceptibility to allergic rhinitis. However, this SNP had a protective effect against development of persistent disease. In patients with asthma, rs315952 in *IL1RA* had a protective effect on the development of the disease [9].

In conclusion, it is suggested that genetic variants in the *TNFA* and *IL1* genes not only affect the risk of developing allergic rhinitis, but are also associated with disease course and severity. Nevertheless, their effect on the clinical phenotype and laboratory findings may be influenced by several factors, such as gender.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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