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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Evaluation of HLA Class II Alleles in Cases with Chronic Spontaneous Urticaria

Kronik Spontan Ürtikerli Olgularda HLA Klas II Alellerinin Değerlendirilmesi

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Abstract

Objectives: Autoantibodies against high-affinity IgE receptor or IgE on the surface of mast cells and basophils are held responsible for etiopathogenesis in some cases with chronic spontaneous urticaria. Factors causing the development of autoimmunity are unknown. Genetic factors are known to play a role in autoimmunity and human leukocyte antigen (HLA) alleles are associated with many autoimmune diseases. Our study aimed to investigate the frequency of HLA class II alleles in patients with chronic spontaneous urticaria.

Materials and Methods: In this cross-sectional study, HLA class II alleles were evaluated in the 80 cases with chronic spontaneous urticaria and in the control group consisting of 100 renal transplant donors. The case group was divided into subgroups by applying autologous serum skin test (ASST). HLA class II alleles were determined in chronic spontaneous urticaria cases with positive and negative ASST and the control group by molecular analysis method (Olerup SSP DQ-DR Combi tray, Genovision, Vienna, Austria).

Results: ASST was found positive in 57.5% of the patients. The frequency of HLA DRB1*04 and HLA DQB1*08 alleles was found to be significantly higher in patients with chronic spontaneous urticaria compared to the control group. In contrast, the frequency of HLA DRB1*07 and HLA DQB1*09 alleles was significantly lower ($p<0.05$). When the ASST positive and negative case groups and the control group were compared, HLA DRB1*04 and HLA DQB1*08 alleles were higher in the ASST positive patient group ($p<0.05$). In the ASST negative patient group, HLA DRB1*01 and HLA DRB1*07 alleles were found in low frequency ($p<0.05$).

Conclusion: The fact that there is a significantly higher frequency of HLA DRB1*04 and DQB1*08 alleles in cases with positive ASST and these alleles do not differ significantly from the control group in cases with negative ASST support the idea that autoimmune mechanisms are responsible for pathogenesis in some of the patients.

Key Words: Genetic Predisposition, HLA Class II Alleles, Chronic Spontaneous Urticaria, Autologous Serum Skin Test, Autoimmunity

Öz

Amaç: Kronik spontan ürtikerli olguların bir kısmında etiyopatogenezden mast hücreleri ve bazofillerin yüzeyindeki yüksek afiniteli IgE reseptörüne veya IgE'ye karşı oluşan otoantikorlar sorumlu tutulmaktadır. Otoimmünitenin gelişmesine neden olan faktörler bilinmemektedir. Genetik faktörlerin otoimmünitede rol oynadığı bilinmektedir ve insan lökosit antijeni (HLA) alellerinin birçok otoimmün hastalıkla ilişkili olduğu gösterilmiştir. Çalışmamızda kronik spontan ürtikerli hastalarda HLA klas II alellerinin sıklığının araştırılması amaçlanmıştır.

Gereç ve Yöntem: Kesitsel tipteki bu çalışmada, 80 kronik spontan ürtikerli olguda ve 100 renal transplant donöründen oluşan kontrol grubunda HLA klas II alelleri değerlendirildi. Olgu grubu otolog serum deri testi (OSDT) uygulanarak alt gruplara ayrıldı. HLA klas II alelleri, OSDT testi pozitif ve negatif olan kronik spontan ürtiker olgularında ve kontrol grubunda moleküler analiz yöntemiyle (Olerup SSP DQ-DR Combi tray, Genovision, Viyana, Avusturya) belirlendi.

Bulgular: OSDT hastaların %57,5'inde pozitif bulundu. Kronik spontan ürtikerli hastalarda HLA DRB1*04 ve HLA DQB1*08 alellerinin sıklığı, kontrol grubuna göre anlamlı olarak daha yüksek tespit edildi. HLA DRB1*07 ve HLA DQB1*09 alellerinin sıklığı ise anlamlı derecede daha düşüktü ($p<0,05$).

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OSDT pozitif ve negatif olgu grupları ile kontrol grubu karşılaştırıldığında; HLA DRB1*04 ve HLA DQB1*08 alelleri OSDT pozitif hasta grubunda daha sık bulundu (p<0,05). OSDT negatif hasta grubunda ise HLA DRB1*01 ve HLA DRB1*07 alelleri düşük sıklıkta saptandı (p<0,05).

Sonuç: OSDT pozitif olan olgularda HLA DRB1*04 ve DQB1*08 alellerinin anlamlı derecede daha sık görülmesi ve bu alellerin OSDT negatif olan olgularda kontrol grubundan anlamlı bir farklılık göstermemesi, hastaların bir kısmında patogenezden otoimmün mekanizmaların sorumlu olduğu fikrini desteklemektedir.

Anahtar Kelimeler: Genetik Yatkınlık, HLA Klas II Alelleri, Kronik Spontan Ürtiker, Otolog Serum Deri Testi, Otoimmünite

Introduction

Urticaria is an itchy disease characterized by erythematous, edematous papules and plaques that develop due to the activation of cutaneous mast cells and the release of histamine and various mast cell mediators; angioedema occurs as a result of temporary edema of the deep dermis, subcutaneous or submucosal tissues (1,2).

According to the disease duration, urticaria is defined as acute urticaria if it lasts for less than six weeks and chronic urticaria if it presents for more than six weeks (1-3).

Chronic urticaria is currently divided into two groups as chronic spontaneous urticaria and inducible urticaria (2,3). The term chronic spontaneous urticaria (previously called chronic idiopathic urticaria) is used for chronic urticaria cases other than urticarial vasculitis, physical urticaria and some diseases associated with urticaria (2-5).

While acute urticaria may develop due to foods, drugs, and infections, the etiological factor cannot be determined in approximately 55-70% of chronic spontaneous urticaria patients (2,3).

In 1986, Grattan et al. (6) showed that erythema and edema response developed with intradermal injection of autologous serum in 60% of the cases with chronic idiopathic urticaria and that serum of these cases induced histamine release from basophils taken from healthy individuals.

This finding was called autologous serum skin test (ASST). In 30-50% of the ASST positive cases, it has been determined that there are IgG antibodies against IgE or the alpha subunit of high-affinity IgE receptors (FcεRIα) found in mast cells and basophils (7). Currently, ASST is used in screening functional antibodies in chronic spontaneous urticaria (3,8). The mechanisms of the development of autoantibodies against FcεRIα and IgE have not yet been revealed. Many autoimmune diseases are associated with human leukocyte antigen (HLA) class II antigens (9). Our study aimed to evaluate the HLA class II antigens in patients with chronic spontaneous urticaria who were ASST positive and negative.

Materials and Methods

A total of 80 cases applied to Ankara University Faculty of Medicine, Department of Dermatology were included in our study. According to the detailed anamnesis, clinical and laboratory findings, the cases had been diagnosed with chronic spontaneous urticaria. ASST was applied to the patients, and the cases were divided into two groups as ASST positive and negative. The control group consisted of 100 unrelated healthy people who were kidney transplant donors. Frequency distributions at HLA DRB1 and DQB1 loci in the control group did not deviate from Hardy-Weinberg equilibrium.

HLA class II alleles were investigated in 80 patients with chronic spontaneous urticaria and the control group at Ankara University Faculty of Medicine, Immunology Laboratory.

Autologous Serum Skin Test

ASST was administered while the patients were active and after their antihistaminic treatment was discontinued for three days. It was confirmed that the patients had not received any immunosuppressive therapy or systemic steroid therapy for at least two months. The separated 0.05 mL serum of patients was injected intradermally in the flexor aspect of the forearm. If the erythema and edema response were 1.5 mm and above compared to the negative control, the test was considered positive (6,10).

Determination of HLA Class II Subgroups

DNA was prepared from blood anticoagulated with ethylenediamine tetraacetic acid obtained from patients and control groups. Puregene DNA isolation kit (Gentra, USA) was used for genomic DNA extraction. Polymerase chain reaction (PCR) (Olerup SSP DQ-DR Combi tray, Genovision, Vienna, Austria) using sequence-specific polymers for each sample was used to identify all the alleles present MHC class II type DRB1 and DQB1 loci. After PCR amplification, the content of each reaction was electrophoresed in 2% gel agar containing 0.5 µL/mL ethidium bromide. It was then imaged under ultraviolet light. All known alleles at the HLA Class II DRB1 and DQB1 loci were detected.

Statistical Analysis

All statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 software (SPSS Inc., Chicago, IL, USA.) HLA-DRB1 and DQB1 allelic frequencies were obtained by direct counting. The distribution differences of HLA class II alleles between the cases with chronic spontaneous urticaria and the control group were evaluated

using chi-square and Fisher's exact tests. ASST positive case group, negative case group and control group were compared among themselves regarding the frequency of HLA class II alleles. Statistical significance (p-value) was calculated for each HLA allele. If the p value was less than 0.05, the difference was considered significant. The odds ratio and 95% confidence interval were calculated to determine the risk of HLA alleles.

Results

In our study, 60 of 80 cases were female (75%) and 20 were male (25%). ASST was positive in 46 (57.5%) of 80 cases and ASST was negative in 34 (42.5%).

When ASST positive and negative case groups were compared, the distribution between genders was not statistically different (p=0.8).

The mean age was 44.1±11.3 years. The mean age of the ASST positive patients was 46.5±10.9 and the mean age of the ASST negative case group was 40.8±11.1 years. The difference in mean age between the two groups was statistically significant (p=0.025).

The mean age of disease onset was 40.7±11.3 years and the duration of disease was 3.3±4.1 years. No statistically significant difference was found between the ASST positive and negative patient groups in terms of age of onset and disease duration (p=0.058, p=0.5).

The angioedema was found in 61 (76.3%) of 80 cases. When evaluated according to the case groups, angioedema was found in 43 (93.5%) of 46 ASST positive cases and 18 (52.9%) of 34 ASST negative cases. The incidence of angioedema was statistically significantly higher in cases with positive ASST than in cases with negative ASST (p<0.01).

When the patients with chronic spontaneous urticaria and the control group were compared according to the results of HLA-class II alleles, HLA-DRB1*04 and HLA-DQB1*08 alleles were higher in chronic spontaneous urticaria, and HLA-DRB1*07 and HLA-DQB1*09 alleles were lower (Table 1).

When the distribution of HLA class II alleles between the ASST positive subgroup and the control group was evaluated, HLA-DRB1*04 and HLA-DQB1*08 alleles were higher in ASST positive case group (Table 2).

According to the comparison of the ASST negative subgroup and the control group according to the distribution of HLA class II alleles, HLA-DRB1*01 and DRB1*07 alleles were lower in ASST negative case group (Table 3).

When ASST positive and ASST negative case groups were evaluated according to the HLA class II alleles distribution, HLA-

Table 1: Distribution of HLA class II alleles in patients with chronic spontaneous urticaria and control group

HLA alleles	Total cases n=80 (%)	Control n=100 (%)	P	Odds ratio	95% CI
DRB1*01	4 (5)	14 (14)	0.046	3.09	0.9-9.8
DRB1*04	**30 (37.5)**	**23 (23)**	**0.034**	**2.0**	**1.04-3.8**
DRB1*07	**9 (11.3)**	**24 (24)**	**0.028**	**2.49**	**1.08-5.7**
DRB1*08	5 (6.3)	3 (3)	0.469	0.46	0.1-2.0
DRB1*09	1 (1.3)	1 (1)	1.000	0.79	0.0-12.9
DRB1*10	6 (7.5)	6 (6)	0.688	0.78	0.2-2.5
DRB1*11	29 (36.3)	37 (37)	0.917	1.03	0.5-1.9
DRB1*12	0 (0)	3 (3)	0.255	1.03	0.9-1.06
DRB1*13	19 (23.8)	15 (15)	0.136	0.56	0.2-1.2
DRB1*14	13 (16.3)	11 (11)	0.303	0.63	0.2-1.5
DRB1*15	13 (16.3)	24 (24)	0.201	1.62	0.7-3.4
DRB1*16	10 (12.5)	10 (10)	0.596	0.77	0.3-1.9
DRB1*17	11 (13.8)	13 (13)	0.883	0.93	0.3-2.2
DQB1*02	18 (22.5)	32 (32)	0.157	1.62	0.8-3.1
DQB1*04	7 (8.8)	5 (5)	0.316	0.54	0.1-1.8
DQB1*05	30 (37.5)	40 (40)	0.732	1.11	0.6-2.0
DQB1*06	28 (35)	32 (32)	0.671	0.87	0.4-1.6
DQB1*07	29 (36.3)	41 (41)	0.516	1.22	0.6-2.2
DQB1*08	**22 (27.5)**	**12 (12)**	**0.008**	**2.77**	**1.2-6.0**
DQB1*09	**1 (1.3)**	**10 (10)**	**0.024**	**8.77**	**1.0-70.1**

CI: Confidence interval, HLA: Human leukocyte antigen

DRB1*04 and HLA-DQB1*08 alleles were found more frequently in ASST positive cases, but this difference was not statistically significant (Table 4).

Discussion

Some patients with chronic spontaneous urticaria have autoreactivity/mast cell activating autoantibodies (2). The ASST is positive in 50-60% of cases with chronic spontaneous urticaria (11). In our study, ASST was found positive in 57.5% of the cases. Studies have shown that patients with chronic urticaria who are positive for ASST have a more severe urticaria course and that angioedema is more common in these cases (11,12). Our study supported these findings.

In the studies conducted on the etiopathogenesis of chronic spontaneous urticaria, The higher prevalence of autoimmune thyroiditis in cases with chronic spontaneous urticaria than the normal population and the higher frequency of autoimmune diseases such as vitiligo, pernicious anemia, insulin-dependent diabetes, and rheumatoid arthritis in chronic urticaria patients with functional autoantibodies support autoimmunity (13,14).

The mechanisms that trigger the development of antibodies in autoimmune urticaria are not yet known. On the other hand, it is known that genetic predisposition is one of the factors that cause autoimmunity. Significantly, the relationship between HLA alleles and various autoimmune diseases has been shown in many studies. Although the relationship between HLA alleles and autoimmunity is not fully understood, there are some hypotheses on this issue (15).

van Neste and Bouillenne (16) investigated the HLA class I allele frequency for the first time in 27 patients with chronic urticaria in 1978 but could not find a difference with the control group.

In other studies investigating HLA class I alleles, Bozek et al. (17) found that HLA-A33 was higher in the control group. Aydogan et al. (18) found that HLA-A24 antigen was higher in the control group and could be protective in chronic urticaria. Doğan et al. (19) in Turkey found the HLA-A allele was high in the control group. They did not detect any statistical difference in HLA-A subgroups. In the studies on HLA B, Bozek et al. (17) and Coban et al. (20) found the HLA-B44 was higher in the patient group and Aydogan et al. (18) found a higher rate of HLA-Bw4 antigen in the patient group.

When studies on HLA class II alleles were examined, the frequency of HLA class II alleles was first investigated by O'Donnell et al. (21). ASST was applied to the cases and histamine release activity with basophils taken from healthy donors of each case's serum were evaluated. In this study, a significant

Table 2: Distribution of HLA class II alleles in ASST positive patients and control group

HLA alleles	ASST positive n=46 (%)	Control n=100 (%)	P	Odds ratio	95% CI
DRB1*01	4 (8.7)	14 (14)	0.365	1.70	0.5-5.5
DRB1*04	**20 (43.5)**	**23 (23)**	**0.012**	**2.57**	**1.2-5.4**
DRB1*07	7 (15.2)	24 (24)	0.228	1.75	0.6-4.4
DRB1*08	1 (2.2)	3 (3)	1.000	1.39	0.1-13.7
DRB1*09	1 (2.2)	1 (1)	0.532	0.45	0.02-7.4
DRB1*10	1 (2.2)	6 (6)	0.433	2.87	0.3-24.5
DRB1*11	15 (32.6)	37 (37)	0.607	1.21	0.5-2.5
DRB1*12	0 (0)	3 (3)	0.552	1.03	0.99-1.06
DRB1*13	10 (21.7)	15 (15)	0.315	0.63	0.2-1.5
DRB1*14	9 (19.6)	11 (11)	0.162	0.50	0.1-1.3
DRB1*15	9 (19.6)	24 (24)	0.552	1.29	0.5-3
DRB1*16	4 (8.7)	10 (10)	1.000	1.16	0.3-3.9
DRB1*17	5 (10.9)	13 (13)	0.716	1.22	0.4-3.6
DQB1*02	10 (21.7)	32 (32)	0.203	1.69	0.7-3.8
DQB1*04	3 (6.5)	5 (5)	0.707	0.75	0.1-3.3
DQB1*05	19 (41.3)	40 (40)	0.881	0.94	0.4-1.9
DQB1*06	14 (30.4)	32 (32)	0.850	1.07	0.5-2.2
DQB1*07	15 (32.6)	41 (41)	0.333	1.43	0.6-2.9
DQB1*08	**15 (32.6)**	**12 (12)**	**0.003**	**3.54**	**1.4-8.4**
DQB1*09	1 (2.2)	10 (10)	0.174	5.0	0.6-40.2

HLA: Human leukocyte antigen, ASST: Autologous serum skin test, CI: Confidence interval

Table 3: Distribution of HLA class II alleles in ASST negative patients and control group

	ASST negative	Control			
HLA alleles	**n=34 (%)**	**n=100 (%)**	**P**	**Odds ratio**	**95% CI**
DRB1*01	**0 (0)**	**14 (14)**	**0.021**	**1.16**	**1.0-1.2**
DRB1*04	10 (29.4)	23 (23)	0.453	0.71	0.3-1.7
DRB1*07	**2 (5.9)**	**24 (24)**	**0.021**	**5.05**	**1.1-22.6**
DRB1*08	4 (11.8)	3 (3)	0.069	0.23	0.04-1.09
DRB1*09	0 (0)	1 (1)	1.000	1.01	0.9-1.03
DRB1*10	5 (14.7)	6 (6)	0.146	0.37	0.1-1.3
DRB1*11	14 (41.2)	37 (37)	0.665	0.83	0.3-1.8
DRB1*12	0 (0)	3 (3)	0.571	1.03	0.9-1.06
DRB1*13	9 (26.5)	15 (15)	0.132	0.49	0.1-1.2
DRB1*14	4 (11.8)	11 (11)	1.000	0.92	0.2-3.1
DRB1*15	4 (11.8)	24 (24)	0.130	2.36	0.7-7.4
DRB1*16	6 (17.6)	10 (10)	0.235	0.51	0.1-1.5
DRB1*17	6 (17.6)	13 (13)	0.571	0.69	0.2-2.0
DQB1*02	8 (23.5)	32 (32)	0.351	1.52	0.6-3.7
DQB1*04	4 (11.8)	5 (5)	0.231	0.39	0.1-1.5
DQB1*05	11 (32.4)	40 (40)	0.428	1.39	0.6-3.1
DQB1*06	14 (41.2)	32 (32)	0.330	0.67	0.3-1.4
DQB1*07	14 (41.2)	41 (41)	0.986	0.99	0.4-2.1
DQB1*08	7 (20.6)	12 (12)	0.256	0.52	0.1-1.4
DQB1*09	0 (0)	10 (10)	0.065	1.11	1.0-1.1

HLA: Human leukocyte antigen, ASST: Autologous serum skin test, CI: Confidence interval

Table 4: Distribution of HLA class II alleles in ASST positive and ASST negative cases

	ASST positive	ASST negative			
HLA alleles	**n=46 (%)**	**n=34 (%)**	**p**	**Odds ratio**	**95% CI**
DRB1*01	4 (8.7)	0 (0)	0.133	1.09	1.0-1.1
DRB1*04	20 (43.5)	10 (29.4)	0.199	0.54	0.2-1.3
DRB1*07	7 (15.2)	2 (5.9)	0.288	0.34	0.06-1.7
DRB1*08	1 (2.2)	4 (11.8)	0.157	6.0	0.6-56.3
DRB1*09	1 (2.2)	0 (0)	1.000	0.97	0.9-1.02
DRB1*10	1 (2.2)	5 (14.7)	0.078	7.75	0.8-69.8
DRB1*11	15 (32.6)	14 (41.2)	0.431	1.44	0.5-3.6
DRB1*12	0 (0)	0 (0)	-	-	-
DRB1*13	10 (21.7)	9 (26.5)	0.623	1.29	0.4-3.6
DRB1*14	9 (19.6)	4 (11.8)	0.350	0.54	0.1-1.9
DRB1*15	9 (19.6)	4 (11.8)	0.350	0.54	0.1-1.9
DRB1*16	4 (8.7)	6 (17.8)	0.310	2.25	0.5-8.7
DRB1*17	5 (10.9)	6 (17.6)	0.514	1.75	0.4-6.3
DQB1*02	10 (21.7)	8 (23.5)	0.850	1.10	0.3-3.1
DQB1*04	3 (6.5)	4 (11.8)	0.451	1.91	0.3-9.1
DQB1*05	19 (41.3)	11 (32.4)	0.414	0.68	0.2-1.7
DQB1*06	14 (30.4)	14 (41.2)	0.319	1.60	0.6-4.0
DQB1*07	15 (32.6)	14 (41.2)	0.431	1.44	0.5-3.6
DQB1*08	15 (32.6)	7 (20.6)	0.234	0.53	0.1-1.5
DQB1*09	1(2.2)	0(0)	1.000	0.97	0.9-1.02

HLA: Human leukocyte antigen, ASST: Autologous serum skin test, CI: Confidence interval

relationship was found with the HLA-DRB1*04 and DQB1*0302 alleles in patients with chronic idiopathic urticaria with ASST positive and *in vitro* histamine release activity. Also, HLA-DRB1*15 and HLA-DQB1*06 alleles were found with a lower frequency in the patient group with chronic idiopathic urticaria. It was suggested that these alleles might play a protective role against the disease (21).

A study conducted in Turkey by Oztas et al. (22) showed that HLA-DRB1*04 was significantly higher in the chronic urticaria group. Coban et al. (20) found that HLA-DRB1*01 and HLA-DRB1*15 alleles were higher in the chronic urticaria group. They applied ASST to the patients; they found no difference in HLA alleles between the ASST positive and negative groups (20). Aydogan et al. (18) found that HLA-DQ1 antigen was higher in the patient group.

Chen et al. (23) found the HLA-DRB1*12 and DRB1*0901 alleles to be high in the patient group, while the DQB1*05 allele was found to be low in the patient group.

Bozek et al. (17) found the HLA-DRB1*04 allele to be high in the patient group, and this difference was found to be highly significant, especially in the OSDT positive group.

In the study conducted by Calamita et al. (24) in 2012, there was no difference between the ASST positive patient group and the control group regarding the frequency of HLA-A, HLA-B and HLA-DR alleles.

Recently, Doğan et al. (19) found no statistically significant difference in the HLA class II alleles in the patient group with chronic spontaneous urticaria and the control group.

We found that the frequency of HLA-DRB1*04 and HLA-DQB1*08 alleles was significantly higher in the chronic spontaneous urticaria cases than in the control group. These results supports the findings obtained from other studies (17,21,22). The fact that the frequency of HLA-DRB1*07 and HLA-DQB1*09 alleles was significantly lower in patients with chronic spontaneous urticaria in our study than in the control group suggests that these alleles may have protective properties for chronic spontaneous urticaria. This finding has not been detected in other studies.

When the frequency of HLA class II alleles was investigated by dividing the cases into two groups as ASST positive and negative, the frequency of HLA-DRB1*04 and HLA-DQB1*08 alleles was found to be statistically significantly higher in the ASST positive patient group, indicating a potential role in the etiology of autoimmunity, compared to the control group. In the ASST negative group, the frequency of HLA-DRB1*04 and HLA-DQB1*08 alleles did not differ significantly from the control group. These findings support O'Donnell et al. (21). Also, HLA-DRB1*04 allele was significantly higher in the ASST positive patient group in the studies of Bozek et al. (17).

Conclusion

The findings obtained from this study show that chronic spontaneous urticaria is a heterogeneous disease and supports that autoimmune mechanisms are responsible for the pathogenesis in some patients. Although the significant relationship detected with the HLA-DRB1*04 allele showed that this may play a role in the pathogenesis of autoimmune urticaria, other genetic or environmental factors that cause the α-chain of the FcεRI receptor to gain antigenicity should be elucidated.

Ethics

Ethics Committee Approval: This manuscript is derived from the thesis conducted in 2005. For this reason, ethical committee approval is not available

Informed Consent: Patients were informed and consent was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.B., Design: A.B., Data Collection or Processing: E.D.S., Analysis or Interpretation: E.D.S., A.B., Literature Search: E.D.S., Writing: E.D.S., A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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