ASSOCIATION BETWEEN MIGRAINE AND ALLERGIC RHINITIS IN CHILDHOOD AND ADOLESCENCE

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ABSTRACT

Objective: *Migraine and allergic rhinitis (AR) represent common childhood and adolescent conditions. The aim of this study to assess AR prevalence, treatment outcome, and clinical issues in childhood and adolescence migraine patients.*

Material and Method: *A total of 146 consecutive patients diagnosed with migraines between November 2012 and May 2014 were included. Laboratory and symptomatic AR assessment, and otolaryngological examinations, were performed. All of the patients were subjected to a detailed neurological examination, and were questioned concerning headaches. The Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire was used for all patients, with scores calculated at baseline (P0) and at third month (P3) and sixth month (P6).*

Results: *Of the 146 total patients, 38 were males (26%) and 108 (74%) were females. Their mean age was 12.19±2.6 years. Only 32 (21.9%) patients were diagnosed with AR. Mean PedMIDAS scores at PO, P3, and P6 were 13.17±8.54, 7.39±5.44, and 9.20±6.76, respectively. Treatment non-compliance rates at P3 and P6 were 11.6% and 26.7%, respectively. The non-compliance rate of AR-positive patients was 5.18-fold higher compared to those negative for AR.*

Conclusion: *We propose that patients followed for migraine should be examined for AR, because treatment compliance is decreased in migraine patients with AR.*

Keywords: *Migraine, allergic rhinitis, headache, PedMIDAS.*
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ÇOCUKLUK VE ADELOSAN ÇAĞINDA MİGREN VE ALLERJİK RİNİT İLİŞKİSİ

ÖZET

Amaç: Çocukluk ve adelosan çağında migren ve allerjik rinit (AR) çok sık birliktelik göstermektedir. Bu çalışmanın amacı adelosan ve çocukluk çağındaki migrenli hastalarda allerjik rinit sıklığını, tedavi sonuçlarını ve klinik yaklaşımlarını değerlendirmektir.

Materyal ve Metot: Kasım 2012 ve Mayıs 2014 tarihleri arasında migren tanısı almış 146 hasta çalışmaya dahil edildi. AR için kulak, burun, boğaz muayenesi, laboratuvar ve klinik değerlendirme yapıldı. Tüm hastalara ayrıntılı nörolojik muayene ve baş ağrısı ile ilgili bir anket yapıldı (PedMIDAS, çocukluk migren maluliyet değerlendirmesi). Tüm hastalara PedMIDAS testi uygulandı ve ilk muayene (P0), üçüncü ay (P3) ve altıncı ay (P6) skorları hesaplandı.

Bulgular: Çalışmaya katılan 146 hastanın 38'i erkek (%26) ve 108'i kız (%74) hasta idi. Yaş ortalaması 12,19±2,6 yıldı. Hastaların 32 (%21,9)'si AR tanısı aldı. PedMIDAS skor ortalamaları sırasıyla P0 (13,17 ±8,54), P3 (7,39±5,44) ve P6 (9,20±6,76) olarak bulundu. Tedavi uyumsuzlukları sırasıyla P3 (%11,6) ve P6 (%26,7) olarak belirlendi. Tedavi uyumsuzluğu AR'li hastalarda, AR olmayan hastalara oranla 5,18 kat daha yüksek bulundu.

Sonuç: AR'si olan migrenli hastalarda tedaviye uyum azaldığı için migren nedeniyle takip edilen hastaların AR için değerlendirilmesini önermekteyiz.

Anahtar kelimeler: Migren, allerjik rinit, baş ağrısı, çocukluk migren maluliyet değerlendirmesi. **Nobel Med 2016; 12(2): 26-30**

INTRODUCTION

Migraine, which represents a combination of neurological, gastrointestinal, and autonomic symptoms, is characterized by severe headaches, and is considered to be the final consequence of a neurovascular process triggered by endogenous and/or exogenous factors in genetically predisposed persons. However, the molecular mechanisms and pathogenesis of migraine remain unclear. The pain observed in migraine is primarily transmitted by trigeminovascular pathways.[1] The trigeminal system may play an integral role in the transmission of pain signals, and in regulating vascular tone. Pain activation during migraine might initiate a cascade of chemical activity from trigeminal sensory nerve endings.[2]

Allergic rhinitis (AR) is a chronic disease of perennial and/or seasonal course, characterized by antibody immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa, triggered by allergens.[3] Migraine prevalence is approximately 35–50% among AR patients; this high rate results in frequent AR patient referrals to pediatric neurology clinics with headaches that are treated unsuccessfully.[3,4] Although there have been several reports concerning migraine frequency among AR patients, no recent studies have addressed AR prevalence in pediatric migraine patients. The frequently overlooked causal link between AR and migraine may result in unnecessary or ineffective treatments.

In this study, AR prevalence was determined among migraine patients referred to our pediatric neurology clinic. We also assessed treatment outcomes and discussed the association between AR and migraine. We aim to raise awareness of this association among pediatricians to avoid ineffective drug treatment and to facilitate the provision of effective combination treatments for migraine patients.

MATERIAL AND METHOD

We included data from 146 consecutive patients diagnosed with migraine at the Pediatric Neurology Department, Pediatric Headache Clinic of the Bezmialem Vakif University (Istanbul, Turkey) between November 2012 and May 2014. The study employed a retrospective design, with data obtained from patient records. The protocol was approved by the Ethics Committee of the medical faculty at Medipol University (Istanbul, Turkey), and procedures were performed in accordance with the Declaration of Helsinki. The criteria of the International Classification of Headache Disorders, 3rd edition (beta version) were used to assess migraine.[5] Patients were evaluated for AR symptoms including nasal congestion, rhinorrhea, sneezing, snoring or mouth breathing, throat drainage, and itchy/watery eyes. Skin allergies and serum IgE levels were measured in patients exhibiting at least one of the above symptoms. Detailed physical examination by an otolaryngologist, to assess for allergic shiners, nasal crease, pale or boggy turbinate, mucous discharge in the nasal passage or postnasal area, or hypertrophy of posterior nasopharyngeal/oropharyngeal wall lymphoid tissues, was then performed. AR diagnosis and treatment was determined by an otolaryngologist. Patients with acute sinusitis, upper respiratory infection, adenotonsillar hypertrophy, trigeminal neuralgia, epilepsy or allergic diseases other than AR were excluded.

The Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire was administered during a 3 month period to evaluate headache-related disability. Total PedMIDAS scores were calculated according to the method described by Hershey *et al.*[6] Patients were classified into the following four groups: Grade I, no or marginal disability (0-10 days); Grade II, mild disability (11-30 days); Grade III, moderate disability (31-50 days) and Grade IV, severe disability (51+days). Each group was further subdivided into allergic rhinitis-positive (AR+) and negative (AR-) patients. Data concerning pretreatment condition, treatment protocols, and response and compliance at P3 and P6 were collected retrospectively. Parents were questioned regarding treatment compliance.

Statistical analyses were performed using the SPSS for Windows software package (ver. 15; SPSS Inc., Chicago, IL, USA). T-test and Mann–Whitney U tests were used to compare groups. Normally distributed variables were expressed as means ± SD; non-normally distributions were expressed as medians and ranges. A p value <0.05 was considered statistically significant. Nonparametric data were compared using Pearson's chi-squared or Fisher's exact test. Multiple comparisons were adjusted using Bonferroni correction and repeated-measures ANOVA. Odds ratios (OR) were used to compare treatment response between the AR (+) and (-) groups.

RESULTS

Of the 146 total patients diagnosed with migraine, 38 were male (26%) and 108 (74%) were female. Their mean age was 12.19±2.6 years (range: 7-17 years); 32 (21.9%) patients were diagnosed as AR. The AR (+) group comprised 20 female (62.5%) and 12 male (37.5%) patients, with a mean age of 12.75±2.75 years. A total of 114 (78.1%) patients were diagnosed as AR (-), of whom 88 were female (77.1%) and 26 were male (22.8%). The mean age of the AR (-) group was 12.02±0.4 years (Table 1). There were no significant

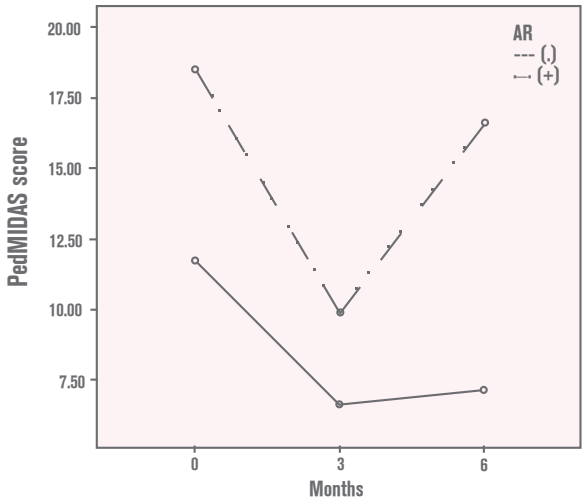

Figure. Comparison of mean PedMIDAS scores between AR (+) and (-)
AR: Allergic rhinitis, **PedMIDAS:** Pediatric Migraine Disability Assessment

Table 1. Mean PedMIDAS scores.

Characteristics	Data
Gender (female)	108 (74%)
AR (+) Female Male	32 (21.9%) 20 (62.5%) 12 (37.5%)
Mean age (n=146)	12.19 ±2.6 years
Mean age AR (+)	12.75±2.75 years
Treatment AR (+) AR (-)	 32/32 (100%) 26/114 (22.8%)
Seasonal AR	18/32 (56.2%)
Perennial AR	14/32 (43.8%)
One- Allergen AR	7/32 (21.8%)
Multiple Allergens AR	25/32 (88.2%)

N: Number, **AR (+):** patients with allergic rhinitis, **AR (-):** patients without allergic rhinitis.

Table 2. Mean PedMIDAS scores.

	P0 (%)	P3 (%)	P6 (%)
Grade 1	58 (39.7)	107 (73.3)	99 (67.8)
Grade 2	81 (55.5)	39 (26.7)	42 (28.8)
Grade 3	6 (4.1)	-	5 (3.4)
Grade 4	1 (0.7)	-	-
Mean	**-13.17±8.54**	**7.39±5.44**	**9.20±6.76**

PedMIDAS: Pediatric migraine oisability assessment, **P0:** pediatric migraine disability assessment scores initially, **P3:** pediatric migraine disability assessment scores on the third month, **P6:** pediatric migraine disability assessment scores on the sixth month.

differences between the AR (+) and AR (-) groups for age or gender (p=0.223 and p=0.187, respectively).

PedMIDAS scores were calculated on the initial (P0), third month (P3) and sixth month (P6) month. The P0 score was used to inform treatment upon admission. Patients with a P0 PedMIDAS score<5 were not provided with any medical treatment, and instead received information pertaining to diet and avoidance of risk factors. All of the AR (+) patients (32/32) received medical treatment for migraine; 22.8% (26/114) of the AR (-) patients were not administered medical treatment and instead only received dietary and general advice.

The P0 scores for grades 1-4 were 39.7% (n=58), 55.5% (n=81), 4.1% (n=6) and 0.7% (n=1), respectively. The mean score for P0 was 13.17±8.54. The P3 scores of grades 1 and 2 were 73.3% (n=107) and 26.7% (n=39), respectively. The mean score for P3 was 7.39±5.44. The P6 scores for grades 1-3 were 67.8% (n=99), 28.8% (n=42) and 3.4% (n=5), respectively. The mean score for P6 was 9.20±6.76 (Table 2). Total PedMIDAS scores were significantly different between AR (+) and AR (-) (p<0.001; Table 3 and Figure). There was also a significant difference between P0 and P3 (p<0.001), and P0 and P6 (p<0.001), but not between P3 and P6 (p=0.336).

In AR (+) patients, a significant improvement was observed between scores at P3 versus P0 (p<0.001), but not between P0 versus P6 (p=0.902). In AR (-) patients, a significant improvement was observed between scores at P0 versus P6 scores (p<0.001), but not between P3 versus P6 (p=0.951; Table 4). Non-compliance rates for all patients at P3 were 11.6% and 26.7%, respectively. The treatment compliance of AR (+) and AR (-) patients was compared at P3 and P6 (Table 5); treatment non-compliance increased commensurate with greater drug use duration, and AR (+) treatment non-compliance was 5.18-fold greater compared to AR (-) (OR=5.18; 95% CI: 1.81, 14.87).

DISCUSSION

This is the first clinical study to report AR frequency among childhood and adolescence patients with migraine; the frequency of migraine among this population has continued to increase, and has been reported at 18.6%.[7] AR prevelance among preschool Turkish children and adolescents has been reported at 44.3% and 49.4%, respectively, and Ku *et al.* reported a migraine prevalence of 35% among adult AR patients.[3,8,9] In a similar study, Ozturk *et al.* demonstrated an even higher prevalence rate of 50%.[4] Although both of these latter two studies were conducted using AR patients, only one report has investigated the association between atopic diseases and AR prevalence rates in adult migraine patients, which were 4.3% and 7.3% in males and females, respectively.[10] Among our patients with migraine, AR prevalence was 21.9%. This difference in AR prevalence between adult and pediatric populations suggests a stronger association between AR and migraine in the latter group. Silanpaa *et al.* assessed patients between 7 and 22 years of age, and reported allergy symptom

prevalence rates of 39.5% and 46.2% in males and females, respectively, thus demonstrating a strong association between allergy symptoms and migraine.[11]

Headache in patients with AR is caused by the activation of mast cells and basophils. In AR, histamine is considered to contribute the development of migraine headaches via increasing the release of nitric oxide (NO). NO is considered to play a role in migraine attacks due to its' vasodilator effects. Additionally, it facilitates the evolution of local neurogenic inflammation by increasing vasodilatation and vascular permeability via H1 and H2 receptors. These mechanisms are important in assessing the relationship of migraine with allergic rhinit.[4]

Patients with migraine were treated with sodium valporate (10 to 15 mg/kg in two divided doses). Sodium valporate does not influence the symptoms of AR. Mometasone furoate monohydrate, single daily dose and montelukast sodium 5 mg, single daily dose were given to the AR patients. Mometasone furoate monohydrate and montelukast sodium don't influence the symptoms of migraine. The P0 PedMIDAS scores of AR (+) patients were markedly higher compared to AR (-) patients, and AR (+) group symptoms worsened over time (P3 vs. P6) to a greater degree compared to the AR (-) group.

AR was also associated with changes in the frequency and severity of migraine attacks. The PedMIDAS scores of AR (+) patients, at baseline and after 6 month of treatments, did not differ significantly (PO-P6) in contrast to the AR (-) group. AR treatment should be provided on a continuous basis. Seasonal changes and increased contact with allergens may exacerbate symptoms, and patients should be encouraged to improve their lifestyle. Martin *et al.*[12] demonstrated that the prevelance and severity of migraine is decreased among AR patients receiving immunotheraphy. The common pathognesis of, and interaction between AR and migraine indicates simultaneous therapy to address both diseases is important.

For pediatric patients, and particularly adolescents, achieving compliance between lifestyle and chronic drug treatment is problematic. During adolescence (11-19 years of age), self-regulatory, and organizational skills are required to manage medication use, which is influenced by several factors including age, extent of knowledge, illness severity, degree of desire for independence, and attitude toward medication.[13] When multiple drugs are prescribed, compliance declines. AR (+) patients were characterized by a 5.18-fold higher non-compliance rate compared to AR (-) patients, which increased from 28.1% at P3 to 37.5% at P6. The majority of the parents surveyed indicated that patients tended to ignored migraine symptoms, and also that daily analgesic use had increased. In contrast, non-compliance rates in AR (-) patients were 7% at P3 and 23.7% at P6. The fact that non-compliance and other drug use data were derived from parents, rather than directly from patients, represents a limitation of the study. Although non-compliance rates increased over time, values at P3 and P6 did not significantly differ. The most frequently cited reason for discontinuing treatment, in AR (-) patients, was a marked decrease in symptom severity. The high prevalence and severity of symptoms in the AR (+) group was associated with greater compliance.

Table 3. Comparison of mean PedMIDAS scores between AR (+) and (-) patients.

	AR (+)	AR (-)	*p*
P0	18.47±9.97	11.69±7.50	<0,001
P3	9.91±6.01	6.68±5.09	0,003
P6	16.63±9.43	7.12±3.79	<0,001

PedMIDAS: Pediatric migraine disabilty assessment, **P0:** pediatric migraine disability assessment scores initially, **P3:** pediatric migraine disability assessment scores on the third month, **P6:** pediatric migraine disability assessment scores on the sixth month, **AR:** allergis rhinitis.

Table 4. Comparison of mean PedMIDAS scores according to duration of ther aphy.

	AR (+) *p*	AR (-) *p*	Total (n=146) *p*
P0-P3	<0,001	<0,001	<0,001
P0-P6	0.902	<0,001	<0,001
P3-P6	<0,001	0.951	0.336

PedMIDAS: Pediatric migraine disability assessment, **P0:** pediatric migraine disability assessment scores initially, **P3:** pediatric migraine disability assessment scores on the third month, **P6:** pediatric migraine disability assessment scores on the sixth month, **AR:** allergis rhinitis.

Table 5. Treatment compatibility rates of AR (+) ve AR (-) patients.

Treatment		(+)		(-)		*p*
Compatibility		**N**	**%**	**N**	**%**	
3. month	AR (+)	23	71.9	9	28.1	0.003
	AR (-)	106	93.0	8	7.0	
	Total	**129**	**88.4**	**17**	**11.6**	
6. month	AR (+)	20	62.5	12	37.5	0.119
	AR (-)	87	76.3	27	23.7	
	Total	**107**	**73.3**	**39**	**26.7**	

N: Number, **AR(+):** patients with allergic rhinitis, **AR (-):** patients without allergic rhinitis.

CONCLUSION

Migraine and AR represent two major diseases impairing childhood quality of life. To the best of our knowledge, this is the first study concerning AR prevalence in childhood and adolescence migraine patients. Exposure to allergens in urban populations

leads to increased migraine symptom frequency and severity, which is in accordance with our observation of an association between AR and migraine prevalence and intensity. In addition, the high level of treatment non-compliance in our AR migraine population suggests that patients referring to clinics with migraines should be examined for AR to potentially reduce drug treatment dose and course.

*The authors declare that there are no conflicts of interest.

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