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Original Article

Atopic disorders are more common in childhood migraine and correlated headache phenotype

Aynur Özge,[1] Nevra Öksüz,[1] Semih Ayta,[3] Derya Uluduz,[4] Veli Yıldırım,[1] Fevziye Toros[1] and Bahar Taşdelen[2]

[1]*Department of Neurology,* [2]*Department of Biostatistics, Mersin University School of Medicine, Mersin,* [3]*Department of Neurology, Maltepe University School of Medicine,* [4]*Department of Neurology, Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey*

Abstract ***Background***: The supportive clinical and pathophysiological data about the correlation between migraine and atopic disorders are far from a coincidence. In order to determine and investigate the correlates of atopic disorders in a specific dataset, we performed this retrospective cross-sectional clinical-based study.

Methods: The dataset was composed from three tertiary center web-based databases (http://www.childhoodheadache.org). Headache diagnosis and differential diagnosis were made according to the International Classification of Headache Disorders, 2nd version and the *Diagnostic Statistical Manual of Mental Disorders*, 5th edition. Migraine with aura, migraine without aura, chronic migraine and episodic and chronic tension type headache (TTH) patients were included. All other causes of headache disorders, including comorbid headache disorders like migraine plus TTH or "possible" causes of headache, were excluded.

Results: The study included 438 patients with migraine and 357 patients with TTH, whose age and sex distribution were identical. After descriptive statistics accordingly, 80 migraine (18.2%) and 23 TTH (6.4%) patients were found to have specific atopic disorders ($P < 0.001$). Atopic disorders are more commonly reported in patients with migraine with aura (21.6%) than those with migraine without aura and TTH ($P < 0.001$). The most common atopic disorders were seasonal rhinitis, conjunctivitis and asthma. There was also a close correlation between TTH with atopic disorders and psychiatric comorbid disorders of the patients.

Conclusions: Although the International Classification of Headache Disorders, 2nd version, does not specify, atopic disorders should be suspected in all migraine patients and their relatives, not only for accurate diagnosis but also for planning prophylactic medications, such as β-blockers.

Key words allergic disorders, atopy, childhood migraine, comorbidity, episodic tension type headache.

Migraine is a common disorder characterized by severe headache accompanied by autonomic and neurological symptoms. Sterile neurogenic inflammation, defects in arachidonic acid or serotonin metabolism, cyclical changes in ovarian steroid concentrations, food allergy, and atopy have been postulated as underlying mechanisms in the peripheral side of the mechanism as well.[1–4] Comorbidity of migraine and atopic diseases, such as eczema and asthma, has been reported previously and this comorbidity has been an important argument for a suspected immune system dysfunction or potential role of neuroinflammation in migraineurs.[1,2,5,6] A large-scale population-based cross-sectional study (The Head-HUNT Study) has confirmed that migraine is associated with respiratory and allergic disorders and these data are supported by other previous reports.[7–9] Episodic tension type headache (ETTH) is a frequent headache subtype in children and adolescents that shares some pathophysiological mechanism with migraine and is a potential transforming risk factor for migraine in adulthood and vice versa.[1,10] ETTH sufferers reported some atopic disorder comorbidities in an adult age group but there was a lower ratio than in a migraine subgroup.[1]

Our previous studies supported the causal correlation between migraine and atopic disorders in different aspects.[1,2,4,11] However, the frequency of atopic features in the Turkish population and potential covariates of having both headache and atopic disorders is still unclear. In order to define frequency, distribution and potential covariates of migraine and ETTH in children and adolescents, we performed this retrospective, clinical-based study.

Methods

The dataset was composed from three tertiary center (the coordinator's center in Mersin and two collaborative centers in Istanbul) web-based databases (http://www.childhoodheadache.org). All of the subjects were questioned face-to-face by the physician for headache disorders. Then they underwent whole neurological examination and completed laboratory investigations if

Correspondence: Aynur Ozge, MD, Department of Neurology, Mersin University School of Medicine, 33079, Mersin, Turkey. Email: aynurozge@gmail.com; aozge@mersin.edu.tr

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necessary. Headache diagnosis and differential diagnosis were made according to the International Classification of Headache Disorders, 2nd version (ICHD-II) and the *Diagnostic Statistical Manual of Mental Disorders*, 5th edition (DSM-5) by a headache specialist (A.O., S.A., D.U.). Migraine with aura (MwA) and without (MwoA) and ETTH diagnoses were made according to ICHD-II. All patients were evaluated by a pediatric psychiatrist on the aspect of psychiatric comorbidity. Psychiatric diagnosis was made according to the DSM-5.[12]

Children and adolescents under 18 years old with a "pure" diagnosis were included in the study. However, all other causes of headache disorders, including comorbid headache disorders like migraine plus TTH or "possible" causes of headache, were excluded. Also, patients with comorbid systemic disorders (i.e. rheumatologic disorders, cancer, etc.) that could have affected this association were excluded from the dataset.

Patients with at least one of the atopic disorders in the last 6 months were included in the atopic disorders group (+A). The following disorders were taken into consideration: asthma; allergic rhinitis; seasonal rhinitis; food allergy; allergic conjunctivitis; and allergic eczema. This evaluation was based only on reports of the parents during to face-to-face interview with the headache specialist. Additional laboratory or clinical investigations were not performed, according to the study design. In this step, asthma diagnosis depended upon the presence of paroxysmal dyspnea attacks supported by pulmonary function test abnormalities, which were verified by a specialist. The allergic rhinitis was described as the presence of such symptoms as itching in the nose, nasal congestion and rhinorrhea, which are characterized by an episodic course. The diagnosis of allergic conjunctivitis was based on episodic symptoms of ocular redness, itching and watering that were not explained otherwise. Signs of rhino-conjunctivitis limited to pollen season and remitting spontaneously were considered in favor of seasonal allergic rhino-conjunctivitis. Finally, a diagnosis of food and drug allergy was made when there was a history of itching, shortness of breath and rash upon exposure to identified agents. Patients without any atopic disorders were included in the no atopic disorders group (−A). This study protocol was approved by the local ethics committee of the coordinator's center (MEU.0.01.00.06/265, 20.10.2008).

Statistics

Descriptive data were summarized as mean, SD and count (percent). Normality assumption for numerical data was detected using the Shapiro–Wilk test. Independent *t*-test was used to compare migraineurs with and without atopic disorders for numerical data, such as headache duration, frequency and severity of the attacks. Independent *t*-test was also used to compare ETTH patients with and without atopic disorders. Univariate analysis of categorical variables was done using the χ^2-test and z-test for two proportions. Covariates of migraine with atopic disorders were evaluated using multiple logistic regression. Similarly, covariates of TTH with atopic disorders were also evaluated using multiple logistic regression. Statistical significance level was 0.05.

Results

After exclusion of the patients as mentioned in the Methods section above, this study included 795 children and adolescents with a mean age of 12.7 ± 3.1 years (range: 4–18 years), 460 of whom were girls (57.8%) and 335 were boys (42.1%). A total of 438 (55.0%) patients were diagnosed as having migraine (21.7% had MwA and 78.3% had MwoA) and 357 (44.9%) were diagnosed as having ETTH.

Distribution of the subgroups and details of headache characteristics are given in Table 1. The study results showed that 80 migraine (18.2% of migraineurs) and 23 TTH (6.4% of ETTH) subjects reported specific atopic disorders ($P < 0.001$). Atopic disorders are more commonly reported in patients with MwA (21.6%) than in those with MwoA and ETTH ($P < 0.001$).[11] The most common types of atopic disorders were seasonal rhinitis, conjunctivitis and asthma. A positive family history of atopic disorders was reported more commonly in migraine sufferers (55.2%) compared to patients with ETTH (51.7%) ($P = 0.356$). Only unilateral localization of the pain was significantly frequent in patients with migraine and comorbid atopic disorders when compared to migraine without atopic disorders. Other headache characteristics did not show significant changes according to having any atopic disorders or not.

Among all patients, 12.42% had psychiatric comorbidity. There was a close correlation between atopic disorders and having psychiatric comorbid disorders of the patients, particularly in the TTH group ($P < 0.001$) (Table 2). We evaluated age- and sex-dependent changes of atopic disorders comorbidity in both migraine and ETTH subgroups. As shown in Table 3, Figure 1a and b, migraine with atopic disorders is more prominent in the 11–14 age groups in both sexes compared to the other age groups ($p_{BOY} = 0.236$, $p_{GIRL} = 0.289$). These data support a possible puberty correlation of this comorbidity. On the other hand, in the ETTH subgroup, atopic disorders comorbidity was most common in children older than 15 years in both sexes.

Regarding phenotypical covariates of migraine, we only found a significant correlation with unilateral localization of headache attacks in the migraine with atopic disorders subgroup (Table 4). On the other hand, the ETTH subgroup showed an important effect of the throbbing quality of attacks and unilateral localization of attacks on having ETTH with atopic disorders comorbidity (Table 5). These data suggest the migrainous phenotype and possible transforming capacity of ETTH subgroups in children and adolescents with atopic disorders.

Discussion

This study shows the important comorbidity of atopic disorders, not only in migraine subgroups but also ETTH sufferers in children and adolescents. These comorbidity changes partially correlated with headache presenting time and also headache phenotype, especially in the migraine subgroup. Puberty has an important effect on the atopic disorders comorbidity of migrainous children. After puberty, ETTH patients showed more atopic disorders comorbidity than younger ones. None of these

Table 1 Demographic features of the study groups (total $n = 795$)

Feature	M + A $n = 80$, 10.0%	M − A $n = 358$, 45.0%	ETTH + A $n = 23$, 2.8%	ETTH − A $n = 334$, 42.0%	P^1, P^2
Age (years)†	12.8 ± 2.7	12.6 ± 3.0	13.3 ± 3.2	12.7 ± 3.3	0.583, 0.398
Headache duration (months)†	21.4 ± 15.3	22.1 ± 16.7	19.1 ± 16.6	20.9 ± 17.5	0.709, 0.635
Duration of attacks (h)†	6.4 ± 7.3	5.8 ± 6.7	6.8 ± 10.1	7.4 ± 11.2	0.510, 0.803
Frequency of attacks (per/month)†	8.6 ± 6.6	8.9 ± 6.8	12.1 ± 7.7	11.3 ± 7.6	0.774, 0.611
Severity of attacks (VAS)†	7.1 ± 1.0	6.8 ± 1.3	6.5 ± 1.5	6.3 ± 5.9	0.113, 0.996
Sex (boy/girl) (*n*, %)	37/43 (46.3/53.8%)	154/204 (43.0/57.0%)	9/14 (39.1/60.9%)	135/199 (40.4/59.6%)	0.598, 0.903
Headache subtype (*n*, %)					
MwA	20 (25.0%)	75 (20.9%)	—	—	0.662
MwoA	60 (75.0%)	283 (79.1%)	—	—	
Quality of pain (*n*, %)					
Throbbing	61 (76.3%)	268 (74.8%)	1 (4.3%)	56 (16.8%)	0.510, 0.222
Non-throbbing	19 (23.7%)	90 (25.2%)	22 (95.6%)	278 (83.3%)	
Unilateral localization of pain (*n*, %)	46 (57.5%)	161 (44.9%)	4 (17.4%)	23 (6.8%)	**0.027**, 0.085
Associated (*n*, %)					
Nausea	27 (33.7%)	91 (25.4%)	3 (13.0%)	26 (7.8%)	0.129, 0.372
Vomiting	23 (28.8%)	74 (20.7%)	—	—	0.116
Photophobia	19 (23.8%)	61 (17.0%)	—	—	0.160
Phonophobia	22 (27.5%)	81 (22.6%)	3 (13.0%)	18 (5.4%)	0.353, 0.131
Osmophobia	12 (15.0%)	53 (14.8%)	—	—	0.972
Vertigo	16 (20.0%)	65 (18.1%)	—	—	0.722
Dizziness	4 (5.0%)	23 (6.4%)	—	—	0.632
Allodynia	3 (3.8%)	8 (2.2%)	—	—	0.434
Triggered by (*n*, %)					
Seasonal changes	7 (8.7%)	21 (5.8%)	2 (8.6%)	11 (3.2%)	0.389, 0.447
Starvation	9 (11.3%)	26 (7.3%)	0	9 (2.7%)	0.234, 0.425
Physical activity	12 (15.0%)	34 (9.5%)	2 (8.6%)	25 (7.5%)	0.147, 0.832

Bold indicates statistical significance. †Values represented as mean ± SD. ETTH + A, episodic tension type headache with atopic disorder; ETTH−A, episodic tension type headache without atopic disorder; M + A, migraine with atopic disorder; M−A, migraine without atopic disorder; MwA, migraine with aura; MwoA, migraine without aura; P^1, comparison of migraine patients with and without atopic disorders; P^2, comparison of tension type headache patients with and without atopic disorders. VAS, Visual Analog Scale.

Table 2. Correlation between atopic disorders and psychiatric comorbid disorders of the patients

	Psychiatric comorbidity		Total *n* (%)	*P*-value
	Yes *n* (%)	No *n* (%)		
M + A	7 (21.9%)	25 (78.1%)	32 (100.0%)	0.345
M−A	19 (15.0%)	108 (85.0%)	127 (100.0%)	
TTH + A	9 (45.0%)	11 (55.0%)	20 (100.0%)	**<0.001**
TTH−A	9 (5.1%)	167 (94.9%)	176 (100.0%)	

Bold indicates statistical significance.

changes showed an important sex effect, but the phenotype maturated with increasing age.

Atopic symptoms are commonly present in patients with migraine headache.[13] Sillanpaa *et al*. reported that 39.5% of boys and 46.2% of girls (age range 7–22 years) with migraine headache reported allergy symptoms.[14] Artto *et al*. found that 25.4% of men and 37.4% of women with migraine headache reported a history of atopy.[15] Our previous study showed that 41.4% of adult migraine subjects had one or more comorbid atopic disorders.[11] This study showed that 18.2% of migraine

Table 3 Age-dependent frequencies of migraine or TTH comorbidities with or without atopic disorders

	Age (years)	Migraine ($n = 438$)		TTH ($n = 357$)		P^1, P^2
		Atopy+ ($n = 80$)	Atopy− ($n = 358$)	Atopy+ ($n = 23$)	Atopy− ($n = 334$)	
Boys	≤10	7 (1.5%)	50 (11.4%)	0 (0%)	36	0.236, 0.096
	11–14	23 (5.2%)	75 (17.1%)	4 (1.1%)	62	
	≥15	7 (1.5%)	29 (6.6%)	5 (1.4%)	37	
Girls	≤10	6 (1.3%)	41 (9.4%)	4 (1.1%)	45	0.289, 0.340
	11–14	25 (5.7%)	92 (21%)	3 (0.8%)	82	
	≥15	12 (2.7%)	71 (16.2%)	7 (1.9%)	72	

P^1 comparison of migraine patients with and without atopic disorders. P^2 comparison of tension type headache patients with and without atopic disorders. TTH, tension type headache.

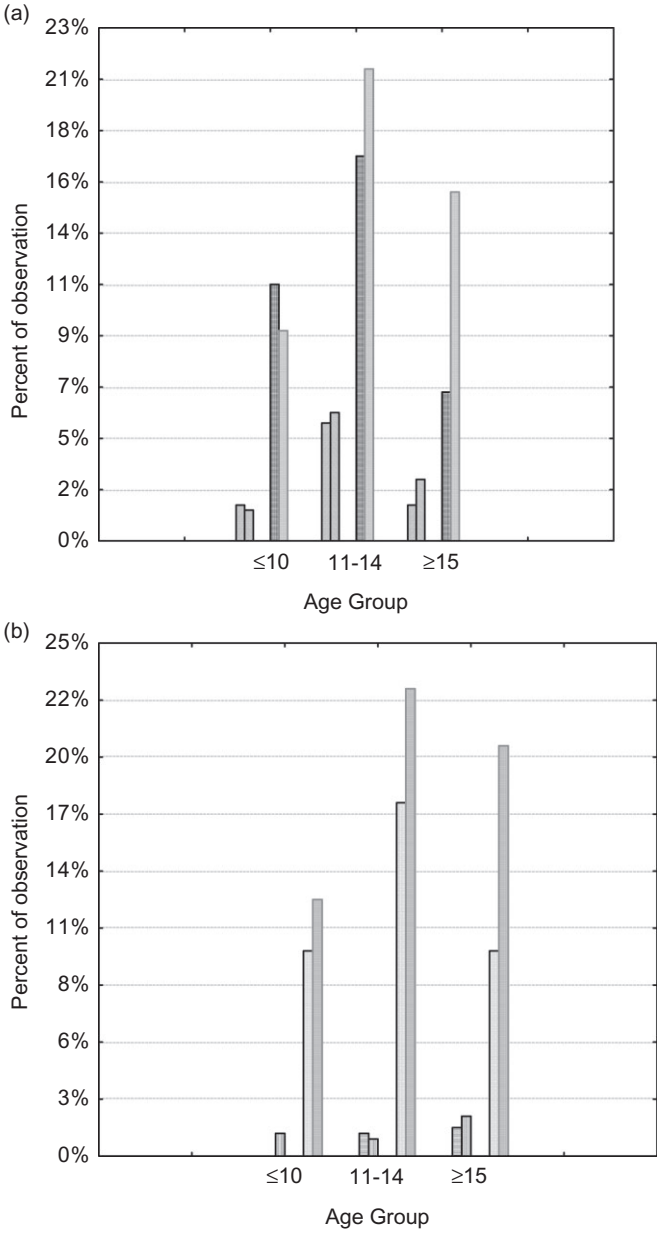

Fig. 1 Age-dependent changes of migraine (a) with and without atopic disorders and (b) tension type headache (TTH) with and without atopic disorders. (a) ■, boy, migraine + atopic disorder; ■, boy, migraine – atopic disorder; ■, girl, migraine + atopic disorder; ■, girl, migraine – atopic disorder; (b) ■, boy, TTH + atopic; ■, boy, TTH – atopic; ■, girl, TTH + atopic; ■, girl, TTH – atopic.

sufferers and 6.4% of ETTH sufferers reported a comorbid atopic disorder, which supports previous reports.

This study tested the effects of atopic disorders on the comorbidity of migraine and ETTH subgroups specifically. To the best of our knowledge, this association has not been evaluated previously. During this analysis we showed an important effect of unilateral pain localization on migraine with atopic disorders comorbidity. The unilateral headache localization and the throbbing headache quality of ETTH sufferers' support the possible transforming characteristics of ETTH to migraine in this age group, as mentioned previously in our epidemiological study.[10]

Table 4 Covariates of migraine with atopic disorders

Variable	Exp B (OR)	95% confidence interval		*P*
		Lower	Upper	
Unilateral localization of attacks	1.865	1.104	3.152	0.020
Associated nausea	1.169	0.581	2.351	0.662
Associated vomiting	1.496	0.811	2.760	0.197
Associated photophobia	1.325	0.643	2.727	0.445
Aggravated by physical activity	1.249	0.566	2.758	0.582

Among the most commonly seen atopic disorders, individuals with active rhinitis symptoms are 2.3 times more likely to suffer from migraine, according to a recent study from the USA.[16] Some reports supported a non-atopic mechanism between migraine and asthma, as confirmed in a very large case–control study with the raised relative risk of 1.59.[3,6] Based on previous data, the comorbidity between asthma and migraine is also evidence supporting an immunological mechanism possibly related to the lowered thresholds of neurogenic inflammations.[1,17,18] An important population-based study showed that allergy does indeed play a role in migraine headaches and that modulation of the allergic response with immunotherapy is associated with a decreased prevalence, frequency, and disability of migraine headaches in younger patients.[9] In a large study, Eross *et al*. confirmed that migraine and other headaches are associated with respiratory and allergic disorders.[19] In this study, 54% of the patients with International Headache Society-defined migraine reported a medical history of allergic rhinitis, and 76% claimed to have had at least one episode of prior acute sinusitis, which are numbers higher than expected in the general population. However, we did not evaluate the effect of immunotherapy in our study design. The most frequent atopic disorder in our study was allergic rhinosinusitis triggered by seasonal changes. The supportive data on the shared relations of the mechanism and phenotype between migraine and ETTH sufferers are far from a coincidence.[1,20,21] Our previous study showed 55.2% of the migraine patients and 51.7% of the ETTH sufferers reported a positive history of atopic disorders. On the other hand, a family history of atopic disorders was reported to be more common in migraine sufferers than

Table 5 Covariates of tension type headache with atopic disorders

Variable	Exp B (OR)	95% confidence interval		*P*
		Lower	Upper	
Throbbing quality of attacks	0.112	0.013	0.982	0.048
Unilateral localization of attacks	4.247	1.169	15.431	0.028
Associated photophobia	2.805	0.359	21.902	0.325
Associated phonophobia	1.947	0.344	11.033	0.451

ETTH sufferers (78.8% vs 21.2%, $P = 0.004$). The most common atopic problems were allergic conjunctivitis, airway disorders, including asthma, seasonal allergy and drug allergies in headache sufferers.[1,22]

Conclusion

The correlations between migraine and comorbid atopic disorders are too common to be coincidental. Supporting our previous studies, this study revealed that atopic comorbidity is important for composing migraine phenotype after puberty, especially in girls. Although the ICHD-II does not specify, atopic disorders should be suspected in all migraine patients and their relatives, not only for accurate diagnosis but also for planning prophylactic medications, such as β-blockers.[3,23]

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Authors' contribution

A.O. was involved in drafting the manuscript and revising it critically for important intellectual content; conception and design, acquisition of data, analysis and interpretation of data; statistical analysis; and has given final approval of the version to be published.

N.O. was involved in data collecting.

S.A. was involved in data collecting, drafting the manuscript and revising it critically for important intellectual content.

D.U. was involved in data collecting and drafting the manuscript and revising it critically for important intellectual content, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

V.Y.: conception and design, acquisition of data, and analysis and interpretation of data.

F.T.: conception and design, acquisition of data, and analysis and interpretation of data. Has given final approval of the version to be published.

B.T.: statistical analysis and commenting of the data.

All authors read and approved the final manuscript.

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