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Brief Communication

Bronchial Hyper-Reactivity in Migraine Without Aura: Is It a New Clue for Inflammation?

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Objective.—We attempted to investigate the relationship between migraine without aura (MwoA) and bronchial hyper-reactivity to postulate inflammation as an underlying mechanism in migraine.

Background.—Comorbidity of migraine and atopic diseases such as asthma has been an argument for suspected immune system dysfunction in migraineurs.

Methods.—Twenty patients with MwoA and 5 control subjects without history of atophy and asthma were included in study. Subjects with abnormal physical examination and chest radiographs were excluded. After a normal spirometry, methacholine bronchoprovocation test was performed in all subjects and controls according to 5 breath dosimeter methods.

Results.—Sixteen of 20 patients and 2 of 5 control subjects were women. Mean ages were 37.5 (19-56) and 33.8 (26-43) years, respectively. Methacholine bronchoprovocation test was positive in 3 patients (15%) but was normal in all controls (0%).

Conclusions.—The relationship between MwoA and bronchial hyper-reactivity may help to postulate the inflammation in migraine as an underlying mechanism.

Key words: migraine without aura, bronchial hyper-reactivity, methacholine, inflammation

Abbreviations: BHR bronchial hyper-reactivity, FEV_1 forced expiratory volume in 1 second, IL-1 β interleukin-1 beta, MPT methacholine bronchoprovocation test, MwoA migraine without aura, PD20 the provocative dose, PFT pulmonary function test, TNF-α tumor necrosis factor alpha

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INTRODUCTION

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 atophy have been postulated as underlying mechanisms. 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 in migraineurs.[1-7] A large-scale population-based cross-sectional study (The Head-HUNT Study) has confirmed that migraine is associated with respiratory and allergic disorders.[8] Individuals with active rhinitis symptoms have suffered 2.3 times more likely from migraine in a recent study from the US.[9] Asthma has been also described as pulmonary migraine and bronchial hyper-reactivity (BHR), which can be shown by

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bronchial provocation tests, is a key feature of asthma.[10-12] Methacholine testing is one of these bronchial provocation tests that can be used for the diagnosis of asthma and also provides an index of the severity of airway reactivity. Comorbidity of migraine and atopic disorders with abnormal pulmonary function test (PFT) results were reported,[13] and these PFT abnormalities in migraineurs can also help to explain the possible relationship between migraine and BHR. In this study, we aimed to investigate the relationship between migraine without aura (MwoA) and BHR and accompanying possible subclinical airway involvement in migraine patients.

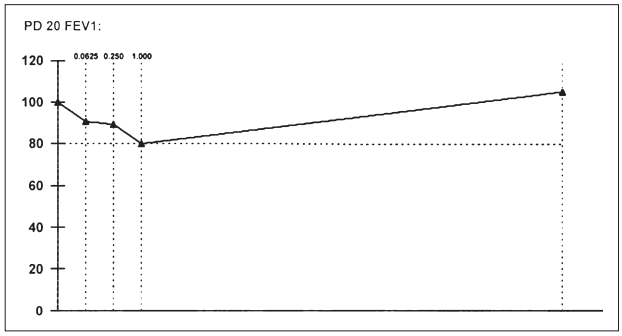

Figure.—A 20% decrease in forced expiratory volume in 1 second (FEV_1) showing positive methacholine bronchoprovocation test with a provocative methacholine dose of 1.0 mg/mL. PD20 = the provocative dose.

METHODS

Patients.—Among the patients followed by the Headache Outpatient Department of Mersin University Hospital, Mersin, Turkey, 20 patients with MwoA and 5 healthy control subjects with no history of atophy and asthma were included in this cross-sectional clinical study. This study was approved by the local ethical committee. Subjects with a history of atophy and asthma, cardiovascular disorders and stroke, hypertension, pregnancy, lactation, viral upper or lower respiratory tract infection within 6 weeks of testing, and current smokers were excluded. Physical examination and chest radiographs were performed and subjects with abnormal findings were not included. All patients and control subjects agreed to take part in the study and signed an informed consent form. Detailed explanations were also made according to the Helsinki declaration. Diagnosis of MwoA was made by the revised International Headache Society criteria[14] and details were obtained from headache diaries. Among atopic disorders, asthma, rhinitis, conjunctivitis, seasonal allergy, food allergy, and drug allergy were taken into consideration. All patients and control subjects were examined by the same chest disease specialist.

Bronchial Provocation Test.—Standardized PFTs were performed in all subjects by using a dry spirometer device (Sensor Medics MPM, Yorba Linda, CA, USA). After a normal spirometry screening and deciding that the subjects have normal pulmonary functions, methacholine bronchoprovocation test (MPT) was performed to all participants according to the guideline of American Thorax Society (1999) by using 5 breath dosimeter methods.[15] Methacholine-serum physiologic solution was administered by nebulisator for 5 different concentrations (0.0625-0.25-1-4-16 mg/mL), the individual took 5 deep breaths of each methacholine concentration and after each concentration a spirometry screening was performed. MPT was terminated when forced expiratory volume in 1 second (FEV_1) decreased 20% of the basal value (the provocative dose or "the provocative dose [PD20]") and at the end of highest concentration. Figure shows a 20% decrease in FEV_1 indicating positive MPT with a provocative methacholine dose of 1.0 mg/mL. The age, gender, pre- and post-FEV_1 values of all 20 patients, and PD20 levels of 3 patients are summarized in Table 1. In MPT negative patients, FEV_1 did not decrease 20% of the basal value and PD20 values could not elicited.

Statistical Analysis.—In order to meet the objectives of the study, a sample size was calculated. As a similar study has not been reported previously to our knowledge, we calculated a sample size of minimum 25 participants with 80% power and 5% type 1 error. After descriptive analysis for age and gender distribution, we performed a Fisher exact test for comparing gender distribution of study groups (MedCalc, v.11.3, BVBA, Mariakerke, Belgium).

RESULTS

Although we have calculated a sample size of minimum 25 patients with 80% power and 5% type 1

Table 1.—The Age, Gender, Pre- and Post-Forced Expiratory Volume in 1 Second (FEV1) Values and the Provocative Dose (PD20) Levels of 20 Patients

Patient number	Age (years)	Gender	Pre-FEV_1 (mL)	Post-FEV_1 (mL)	Alteration (%)	PD20 (mg/mL)
1	29	Female	3570	3200	–10	—
2	46	Female	2940	2440	–17	—
3	47	Female	3140	2510	–20	1.0
4	56	Female	3030	2970	–2	—
5	19	Male	4870	4560	–7	—
6	29	Female	2690	1550	–42	1.0
7	48	Female	2910	2550	–12	—
8	47	Female	2670	2120	–20	4.0
9	44	Male	5130	5080	–1	—
10	39	Female	2720	2430	–10	—
11	24	Female	4090	4200	+2	—
12	26	Male	4980	4560	–8	—
13	46	Female	2740	2550	–7	—
14	34	Female	2630	2730	+4	—
15	44	Female	2710	2620	–3	—
16	35	Female	3600	3560	–1	—
17	38	Female	3210	3140	–2	—
18	32	Female	3330	3290	–3	—
19	42	Female	2350	2470	+5	—
20	24	Female	3650	3550	–3	—

error, MPT could be performed in only 20 patients and 5 healthy controls because of the invasive methodology and strict inclusion criteria. Sixteen of 20 patients and 2 of 5 control subjects were women. Mean ages were 37.5 (19-56) and 33.8 (26-43) years, respectively. The study groups were age matched ($P > .05$, Fisher exact test). In patient group, MPT was positive in 3 female participants (15%). There was no MPT positivity in control subjects. The mean value of decrease in FEV_1 was 9.6% in patient group and 6.8% in control subjects. In MPT positive patients, methacholine PD20s were 1.0 mg/mL, 1.0 mg/mL, and 4.0 mg/mL, respectively. The categorization of bronchial responsiveness is shown in Table 2. If PD20 is >16 mg/mL, it may be stated with a high degree of confidence that the patient does not currently have asthma. If PD20 <1.0 mg/mL, the test provides strong confirmation of the clinical diagnosis of asthma. When the PD20 is between 1 and 16 mg/mL, one must be more cautious about stating whether or not the patient has asthma.[15] In our patient group, the PD20 values were between 1.0-4.0 mg/mL, showing that these patients do not currently have asthma but a possible airway inflammation.

DISCUSSION

Based on the many studies about the association of migraine and atophy, it is understandable that migraine is already linked to a hypersensitive immune system.[16] MPT can be used for the diagnosis of asthma and also provide an index of the severity of airway reactivity. Despite controversies, asthma has generally been found to be associated with migraine.[17,18] But the relationship between migraine (vascular reactivity) and asthma (bronchial reactivity) was thought to be independent from atopic mechanisms. The combined functional abnormalities

Table 2.—Categorization of Bronchial Responsiveness (15)

PD20 (mg/mL)	Interpretation
>16	Normal bronchial responsiveness
4.0-16	Borderline BHR
1-4.0	Mild BHR (positive test)
<1.0	Moderate to severe BHR

BHR = bronchial hyper-reactivity; PD20 = the provocative dose.

in smooth muscles of vessel and airway walls should be a possible explanation.[1] The results of our study have demonstrated that BHR is more common in patients with MwoA (15%) than the healthy controls (0%). Although number of participants was too small to comment about gender difference, all of the MPT positive patients were female in our study. The prevalence of BHR in females is generally 2-3 times higher than that in males in studies in which stratification by gender was reported. A possible explanation is related to differences in baseline airway calibers of females. Lower baseline airway calibers of females may be more likely to have a positive response to methacholine because of anatomical differences.[19] In our MPT positive patients the PD20 values were between 1.0-4.0 mg/mL, showing that these patients do not currently have asthma but a possible airway inflammation. This condition was observed in the absence of clinical, radiological, and functional evidence of airway disease.

Positive MPT can be seen in also allergic rhinitis, bronchiectasis, chronic obstructive pulmonary disease, cystic fibrosis, hypersensitivity pneumonitis, left ventricular failure, lung and heart transplantation, sarcoidosis, tropical pulmonary eosinphilia, viral upper or lower respiratory tract infection within 6 weeks of testing, and rarely in normal subjects.[20] But none of our participants had history or clinical features of these diseases. MPT is a predictor of risk for developing asthma later in life or sign of previous asthma.[21] But varying of the response in the same person because of the breathing pattern (tidal breathing or big breath) used to deliver the agent is a disadvantage of this method. Negative test in symptomatic patients is useful to exclude asthma but does not exclude exercise-induced asthma. Positive test is not specific for asthma as it can also be observed in people with airflow limitation or airway remodeling. But all of our participants had normal physical examination and chest radiographs without a history of atophy and asthma. Positive test also occurs with airway injury,[21] but none of the participants had airway injury.

Bartholo et al reported that MPT was found in 27% of patients with Crohn's disease and none of the control subjects. There were also increased lymphocytes in sputum of these patients with Crohn's disease suggesting the presence of an inflammatory response at respiratory tract.[22] Vigorous activation of CD4 cells in the intestinal mucosa of patients with active Crohn's disease was previously reported.[23] Recent studies have suggested that the common mucosal immune system may be involved in various T-lymphocyte mediated disorders. Tracheal involvement may be seen in Crohn's disease as an unusual finding and consists of mucosal inflammation.[24-26] T-lymphocyte cells also have a role in pathogenesis of asthma.[27] This might represent the existence of a minimum inflammation level from which the MPT would become positive. This inflammatory response may suggest the sterile neurogenic inflammation as one of the underlying mechanisms of migraine.

In a recent study, Özge et al reported that 41.4% of 186 migraine patients had at least one atopic disorder. Comparison of PFT variables between the migraine with atophy, migraine without atophy and control groups showed important limitations of the airway, especially in migraine with atopic disorders group.[13] Tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1 β) are 2 of the well known mediators that play key role in the pathogenesis of asthma.[28,29] In another recent study, Yılmaz et al showed TNF-α 308 G/A and IL-1 β + 3953 C/T polymorphisms in patients with MwoA suggesting the role of inflammatory cytokines in migraine generation.[30] As mentioned above, these cytokines are also related to the pathogenesis of asthma and our study may suggest a new clue about MwoA and inflammation by the association of BHR.

The limitation of this pilot study was low number of patients. But as the methodology was invasive and inclusion criteria were strict, more MPT could not be performed.

CONCLUSIONS

To our knowledge, it is the first time that a possible relationship between MwoA and BHR is shown. However, data of this pilot study were obtained from a small sample and BHR were shown in 15% of patients. It can be robust to conclude that this association is a reflection of inflammation playing a role in MwoA. But this possible relationship may be helpful

in evolving new treatment strategies for migraine by preventing the inflammatory response or altering the TNF-α and IL-1 β levels. To our knowledge, there are not any reported *in vitro* or experimental approaches about this hypothesis. Experimental approaches can be used to move this hypothesis forward with adequate sample sizes. In order to prevent probable respiratory tract disorders in migraineurs, clinicians should be also alert to these alterations.

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