A CORRELATION BETWEEN MIGRAINE, HISTAMINE AND IMMUNOGLOBULIN E.

Parisa Gazerani*, Zahra Pourpak**, A. Ahmadiani*, A. Hemmati***, A. Kazemnejad****

* From the Department of Neuroscience Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, 19835-355, Iran.
** Allergy, Asthma and Immunology Research Institute, Tehran University of Medical Sciences, Tehran, Iran.
*** Neurology Department of Shohada Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.
**** Department of Biostatistics, Tarbiat Modares University, Tehran, Iran.

ABSTRACT

Although migraine affects about 15% of the population, and many studies have been performed to find the mechanism and successful management, the physiopathology of migraine is still largely unknown. The possibility of an IgE-mediated allergic mechanism and the role of histamine remains controversial.

The aim of the present study was the evaluation of serum total IgE and histamine levels in migraine patients and the influence of allergy on them.

70 patients (18-58 years) with migraine without aura were divided into 2 groups according to their history of allergy (60% with & 40% without allergy). Serum samples were collected during fasting without allowing any premedication in 2 conditions of attack and remission periods. There was a control group containing 45 healthy volunteers. Serum total IgE and histamine levels were measured by ELISA and fluorimetric methods respectively.

Mean and standard error of serum histamine (ng/ml) and total IgE (IU/ml) levels were found in control group as 48.16±2.70, 38.31±3.20 and in migraine with an allergy group as 159.11±4.60, 303.30±42.50 and in migraine without an allergy group as 105.01±8.50, 79.07±2.70 respectively.

* Corresponding author: Abolhassan Ahmadiani, Pharm.D., Ph.D.
Neuroscience Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, 19835-355, Iran.
Fax: +9821-2403154
E-mail: aahmadiani@yahoo.com
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Total IgE levels in migraine group with allergy were found significantly (P<0.0001) above the control and another group suggesting an influence of an IgE-mediated mechanism on migraine. Plasma histamine levels were significantly elevated (P<0.0001) in patients with migraine both during headache and symptom-free periods compared with control group although it shows that there is an increased susceptibility to histamine in allergic conditions, nonetheless this molecule has also an unrelated role in migraine.

The relationship between allergy and migraine can be based in part on IgE-mediated mechanism, with histamine release playing an important role.

Thus avoidance of allergic conditions in migraine patients may be a simple helpful way to prophylaxis or their treatment.

Keywords: Histamine. Total IgE. Allergy. Migraine

INTRODUCTION

Migraine is a complex neurological disorder that affects about 15% of the population and can be disabling (1). In the last 10 years, much progress has been made in understanding the molecular basis of migraine dictating new approaches to the pharmacological treatment (2). Successful management of migraine headache involves identifying and avoiding headache triggers and using appropriate abortive or prophylactic treatment once migraine is recognized, but the physiopathology of migraine is still largely unknown (3). The correlation between allergy and migraine has been discussed for many years, while the possibility of an Immunoglobulin E (IgE) - mediated allergic mechanism in migraine remains controversial (4). Many studies have been found to be of great interest in elucidating the possible correlation between migraine and allergy, specially food allergy (5-8). It has been reported that food-induced migraine is not IgE-mediated but caused by histamine (9). On the other hand, some studies suggested that the relationship between food ingestion and migraine could be based in part to an allergic mechanism (8,10). There are some evidences which show that free histamine diet or avoiding of some allergens such as inhalants or environmental allergens, can eliminate or abolish headache periods without the need for long term medications, especially in pediatrics (9,11). The mechanism may be inhibition of initial contacts of allergen leading to produce IgE which can sensitize mast cells to release histamine (12).

Histamine has an important role in allergic conditions, and in atopic patients who have elevated IgE levels, increased histamine levels have been found (13). Active challenges can lead to elevation of serum histamine levels while placebo challenges don’t show such an effect (7,14,15). Based on vascular theory of migraine, histamine can also cause pain being a powerful vascular relaxant (16). Also there are some evidences of elevated histamine in plasma or its metabolites in urine, and its precursor (histidine) in cerebrospinal fluid of migraine patients (17,18). Most recently, it has been suggested that during migraine attacks, some neuropeptides, which have been released from brain nerve endings, influence some special mast cells which have been located around those neurons - such as meninges- leading to histamine release (19) like IgE effects on local mast cells (14).
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On the other hand, it has been found that H1-antagonists such as mepyramine can abolish immediate and delayed migraine attacks which can explain the probable role of histamine in migraine pain (20,21).

The injection, inhalation or use of histamine agonists, also can cause a migraine-like headache or aggravate migraine attacks in patients (22-24).

Based on these findings, we decided to find a correlation between migraine, IgE-mediated conditions and histamine. Since most of the studies in regard have been focused on the influence of allergen avoidance and hypoullergen diets in migraine patients, in the present study, it has been tried to determine the serum total IgE and histamine levels in two groups of migraine patients (based on their positive or negative history of allergy).

**MATERIALS & METHODS**

**Patients**

Seventy volunteer patients referred to Tehran Shohada Hospital from March to November, 2000 (55 female, 15 male), age ranged 18-58 years suffering from migraine without an aura-according to IHS (International Headache Society) criteria-(25) were selected and divided into 2 groups based on their history of allergy (Asthma, Rhinitis, Eczema, Urticaria). In this way there were 60% with and 40% without a history of allergy. One healthy control group (38 female, 7 male), age ranged 20-50 years without a history of allergy or migraine, was included as volunteers after explaining the aim of the study.

Prior to inclusion, all underwent a battery of examinations to clinch the diagnosis of migraine suffice it to say that infectious diseases or a history of allergy were ruled out.

**Sampling**

Blood samples (3 ml) were withdrawn from a cubital fossa vein in 2 phases of pain and at least during 48 hours relief period from pain in migraine sufferers. Patients were fasting except for taking their medications 24 hours before sampling. Samples were collected in dried acid-washed glass microtubes labeled with the name, date, group of patient and phases of pain and remission. Serum was separated by centrifugation in 4000g for 10 min and then divided in two portions, one being placed in polyethylene sealed microtubes frozen at -20°C until reading for IgE and another deproteinated with perchloric acid (0.1 ml for each ml of serum) for histamine measurement under the same conditions. Histamine and IgE measurement were performed within 15 days after sampling.

**Histamine and IgE Measurement**

Histamine content was measured using a modified fluorimetric method diagram 1 (26). Serum total IgE was determined by ELISA method using special kits (prepared by Binding Site Co. Italy).

**Statistical analysis**

Results were expressed as mean SE (Standard Error). Statistical comparisons were performed using the following statistical tests:

- Kolmogorove - Smirnov test for investigation of normal distribution.
- Analysis of Variance (ANOVA) and Tukey, LSD Post Hoc for comparison between groups.
- Kruskal - Wallis test for non-parametric comparisons.
- T-test for comparison between two groups (migraine patients and healthy group)

**RESULTS**

All variables had normal distribution (according to Kolmogorov - Smirnov test) except IgE in allergic migraine group which had not a normal distribution (P<0.003).

Both serum total IgE and histamine levels in migraine patients, were found significantly (P<0.0001) higher than in the normal healthy group (Fig. 1,2 respectively). Also a marked elevation of serum histamine (P<0.06) and total IgE (P<0.0001) levels in allergic group compared with non allergic group was observed (Fig.3,4 respectively).

Serum histamine levels were significantly (P<0.0001) increased in the pain phase compared to the period of remission (Fig.2).
Migraine, Histamine and IgE

Diagram 1. Histamine assay by an improved fluorimetric method

1 ml sample (blood or serum) + 0.9 ml D.W. + 0.1 ml perchloric acid 60%

↓
Mix & Centrifuge

↓
0.8 ml aliquot + 0.1 ml NaOH 5M + 300 mg NaCl + 2 ml butanol

↓
Mix & Centrifuge

↓
aqueous phase removed + butanol phase + 1 ml NaOH 0.1 M

↓
Mix & Centrifuge

↓
aqueous phase removed + 1.6 ml butanol phase
0.9 ml HCl 0.1 M
2.8 ml heptan

↓
Mix & Centrifuge

↓
butanol phase removed + aqueous phase

↓
Sample

↓
Blank

↓

0.4 ml
0.08 ml NaOH 1 M
0.02 ml OPA
0.04 ml HCl 3 M

0.4 ml
0.08 ml NaOH 1 M
0.06 ml HCl 3 M
0.02 ml OPA

↓
↓
↓
↓
↓
↓

Mix & Read in 360 nm ex. & 450 nm em. wavelength

OPA: o-phthalaldehyde
D.W.: Distilled water
Fig. 1. Serum total IgE levels (IU/ml) in allergic and non-allergic migraine patients. (***P<0.0001)

Fig. 2. Serum histamine levels (ng/ml) in migraine patients during pain and pain relief. (***P<0.0001)

The correlation coefficient between histamine in pain group and control was -0.14 with a p value of 0.37. The correlation coefficient between IgE and histamine in non-allergic group - in pain phase - was +0.14 with a p value of 0.46 and between IgE and histamine in non-allergic group - in relief of pain - was +0.30 with a p value of 0.11. In allergic group the Spearman coefficient was used. The correlation between histamine in pain phase and IgE was -0.05 with a p value of 0.70 and between histamine in no-pain phase and IgE was -0.09 with a p value of 0.55. Therefore there were no correlations between histamine and IgE levels in all the groups.

Findings have been summarized (Table 1).

DISCUSSION

The studied group comprised of 70 patients complaining of headache and referred to the neurology clinic, who were diagnosed as migraine sufferers. Then on the basis of history of allergy, 2 groups were isolated (60% with and 40% without allergy) as shown in Table 1. It has been reported that among migraine patients age ranged from 11-17 years, in 40% cases, migraine was associated with a history of allergy (4). The percentage of migraine patients with a positive history of allergy was higher than non-allergic persons. Meanwhile, probably the incidence of migraine was higher when allergic conditions existed. Such findings, can support this view that obtaining a history of allergy at the beginning of the diagnosis and treatment, may be helpful for effective prophylaxis or medications in migraine sufferers.

There are some reports on changes of immunoglobulines, complement factors, mediators, cytokines and inflammatory cells in migraine attacks, suggesting an involvement of immunological mechanisms in physiopathology of migraine (6). The findings also indicated that the mean total IgE levels in both groups of migraine patients were significantly (p<0.0001) increased compared to that of healthy subjects (Fig.1). It seems that in migraine sufferers, probably additional factors affect IgE production. On the basis of these findings, remarkable (p<0.0001) increases of IgE in allergic group (Fig.3) can indicate a higher sensitivity of immune system in these patients. There are some evidences which show that a special food diet or environmental factors aggravate the headache in allergy-induced migraine. In these cases, restricted diet or avoidance of trigger factors especially in pediatrics has produced a noticeable cure (7,11,26). Also it has been suggested that the elevated IgE levels in migraine patients with a positive allergic history, may be due to the influence of genetic factors on IgE production (28).

Regarding these findings, distinguishing allergic migraine patients and using anti allergic treatment for them, may restrict their attacks or abolish the course of headache. This is viewed as a successful prophylactic modality in pediatric patients as depicted in our previous study (29).
Migraine, Histamine and IgE

Table 1. Summary of serum total IgE (IU/ml) and histamine (ng/ml) in control, non-allergic and allergic migraine patients.

<table>
<thead>
<tr>
<th></th>
<th>Serum total IgE (IU/ml)</th>
<th>Serum histamine (ng/ml)</th>
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<tbody>
<tr>
<td></td>
<td>Mean±SE</td>
<td>Min</td>
</tr>
<tr>
<td>Control</td>
<td></td>
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</tr>
<tr>
<td>(n=45)</td>
<td>38.31±3.20</td>
<td>9.00</td>
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<tr>
<td>Non-allergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=28)</td>
<td>79.07±2.70</td>
<td>45.00</td>
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<td></td>
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</tr>
<tr>
<td>Allergic</td>
<td></td>
<td></td>
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<tr>
<td>(n=42)</td>
<td>303.30±42.50</td>
<td>46.00</td>
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- SE: Standard error, Min: Minimum, Max: Maximum, CI: Confidence Interval, P: Pain, NP: No-pain

Fig. 3. Serum total IgE levels (IU/ml) in allergic and non-allergic group. (**P<0.001)

As has been shown in the findings, serum histamine levels were significantly (p<0.0001) elevated in migraine patients during symptom-free and headache attack compared with healthy subjects (Fig.2). Elevated basic serum histamine levels in migraine patients, may be because of a continuously basic stimulation on prevascular nerve endings, which can cause histamine release directly or via other mediators.

It has been reported that injected histamine, inhaled histamine, histamine agonists and histamine liberators often cause headache particularly and severely in migraine patients (22,23). Also it is of interest that migraine sufferers are reported to have increased basal gastric acid levels and an increased incidence of peptic ulcers, which is conceivable that free circulating histamine may be responsible for those effects (17).

Therefore elevated basic serum histamine levels in migraine patients, as shown in our findings, may be the cause of enhanced sensitivity to additional histamine than normal subjects. There are some reports on elevated histamine metabolites in urine and histidine in cerebrospinal fluid of migraine patients suggesting the presence of increased quantities of free histamine in these patients (17,18).

In pain phase of two groups of migraine patients, significant (P<0.0001) rise of serum histamine levels was observed (Fig. 2) It seems that certain stimuli such as IgE-mediated reactions, stress, starvation, insomnia probably initiate more stimulation, leading to an additional histamine release.

Findings in migraine allergic group suggest that although there is an increased susceptibility to histamine in allergic conditions, histamine also plays an unrelated role in migraine pain, because in non-allergic patients it has elevated significantly.
CONCLUSION

The relationship between allergy and migraine can be based in part on IgE-mediated mechanism, with histamine release playing an important role. Thus avoidance of allergic conditions in migraine patients may be a simple helpful way for prophylaxis or treatment.

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