

Influence of allergic rhinitis in children and adolescents with recurrent headache

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
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Article history: Received: 04.01.2018 Accepted: 11.01.2018 Published: 30.04.2018

ABSTRACT:

Introduction: Migraine and allergies are common occurrences. The aim of this study was to investigate the relationship between respiratory allergy and cephalalgic migraine in childhood.

Materials and Methods: We screened 800 children for headache and its characteristics. After that we investigated the presence of allergy performing prick tests, rhinoscopy, endoscopy, rhinomanometry, nasal cytology and mucociliary clearance tests.

Results: Out of 800 children screened, 96 suffered from headache. Among these, 67 resulted to suffered from both headache and allergy. We found a significant correlation between allergy and headache onset in the morning and headache onset in the evening in non-allergic subjects. The average duration of the a headache attack was independent from the presence of allergy, as well as the frequency of the cephalalgic attacks, and the localization of the pain. Prodromal symptoms connected with headache were reported to be: dizziness, aurea, sparkling scotoma, nausea and vomiting, and they were associated with absence of allergy. We also found a relationship between female gender and headache onset, but in teen-agers only. Paracetamol or FANS were used in the majority of cases, but antihistaminic therapy and/or nasal topical sprays were also reported.

Discussion: For an effective diagnostic and therapeutic approach to migraine, the pediatrician should take into account atopy and its related allergic manifestations requiring a consultation with an otolaryngologist or allergist, if necessary. Our findings also stress the potential role of medicines that are not usually utilized for migraine attacks, such as antihistamines or decongestant nasal sprays.

KEYWORDS:

migraine, allergic rhinitis, cephalgia, allergy, headache

INTRODUCTION

Allergy and headache are common pathologies both in adult and in children. Prevalence of migraine in pediatric population ranges from 3.3% to 21.4%; it is higher in females and it increases from childhood to adolescence. [1] [2] [3]. Whereas, according to the International Study on Asthma and Allergy in Childhood, the prevalence of allergic common manifestations like asthma, allergic rhino-conjunctivitis, and atopic eczema is 8.1% among children aged between 6 and 7 years old and 10.5% among children aged 13-14 years. [4] [5] Allergic respiratory manifestations include allergic rhinitis symptoms like

nasal discharge, sneezes, pricking nose, lachrymation and respiratory difficulties with asthmatic bronchospasm and glottis or tongue edema.

Cephalalgic migraine is characterized by headache that can be associated with visual and vagus nerve symptoms (scotomas, aurea, nausea, vomiting). Often the migraine pain attack is preceded by prodromal symptoms such as dizziness or vertigo, sparkling scotomas, visual impairment. Both headaches and allergies are common in children and teenagers and they can cause significant distress and disability for young patients and their families. [6]

Tab. I. Questionnaire to investigate headache**PRESENCE OF HEADACHE IN CHILDREN AND ITS FEATURES**

Name Date of birth Sex

1. Does your child suffer or has suffered from headache?

Yes	No
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If you answer "No" please do not continue filling the questionnaire.

2. Mode of onset. When the cephalalgic attack occurs?

Morning	Afternoon	Evening	Night
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3. Duration. How long does the cephalalgic attack last?

About an hour	Between 2 and 6 hours	More than 6 hours
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4. Frequency. How many times does the cephalalgic attack occur?

More than twice a month	Once or twice a month	Less than once a month
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5. Localization of pain. Where is the headache pain predominantly localized?

Frontal head region	Parietal head region	Diffused	Other
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6. Presence of warning signs. Is the cephalalgic attack preceded by warning signs?

Yes	No
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What warning signs occurred?

Aurea/Scotoma	Visual impairment	Nausea/vomiting	Dizziness
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7. Adopted therapies. What therapy/therapies is/are taken during or before the cephalalgic attack?

Paracetamol/FANS	Nothing	Other (specificate)
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8. Familiarity. Are there family members who suffer from headache?

Mother	Father	Both	No
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Several studies have documented the association between migraine and various comorbidities or psychosocial factors. In particular, many studies have reported associations between migraine and atopic disease such as food allergy, asthma, or allergic rhinitis. [3] [7] [8] [9] [10]

The aim of this study was to investigate the relationship between respiratory allergy and cephalalgic migraine in childhood.

MATERIALS AND METHODS

Between January 2016 and December 2016, a questionnaire

(Tab. I.) was submitted to 800 pediatric patients (411 males and 389 females) aged from 6 to 17 years (average 14 years). The questionnaire, to be filled with the help of parents, was meant to assess the presence of headache and to analyze its characteristics (mode of onset of pain, duration, monthly frequency, localization, presence of warning signs, adopted therapies and family history of headache). After establishing that 96 out of 800 pediatric patients had a positive anamnesis for cephalalgic symptoms, we decided to screen this sample for the presence of allergy, performing prick tests in accordance with international guidelines (Tab. II.). [11] [12] After that, patients underwent a standard diagnostic procedure, including anterior rhinoscopy, nasal endoscopy, rhinomanometry, nasal

cytology for the study of nasal cells population and mucociliary clearance. [13] [14]

Anterior rhinoscopy was performed using pediatric diagnostic tools. We observed colour and trophism of septal mucosae and inferior turbinates, presence and features of nasal discharge, possible presence of nasal polyposis, since according with international studies, certain findings -such inferior turbinate hypertrophy or aqueous discharge- suggest the presence of allergic rhinitis. [15]

Before performing nasal endoscopy, two/three drops of Tramadolina Chloridrate were applied to each nostril; five minutes later, nasal examination was carried out by an expert otolaryngologist with a flexible nasal endoscope, 2.4 mm diameter, in accordance with international reports. [16] [17]

To perform rhinomanometry patients were asked to wear a face mask, close their mouth and breathe only with the nose in accordance with the International Committee on Standardization of Rhinomanometry. [18] [19]

A retest was performed in all patients. The results of rhinomanometry were considered related to nasal flows of 150 Pa and compared with pediatric reference values. height-dependent reported in literature [18] [20]. The normality threshold is set at 0.5 Pa/mmc at 150 Pascal pressure, and values below this level were considered within the range of normality contrariwise, upper values suggest obstructive nasal flow.

Flow expressed in cc/sec and resistance expressed in Pascal were measured for the right and left nasal fossae and as overall value. Total resistance was calculated combining the resistances of the two nostrils according to the formula [21] [22]:

$$R_{\text{tot}} = (R_{\text{left}} \times R_{\text{right}}) / (R_{\text{left}} + R_{\text{right}})$$

In accordance with Zapletal et al. [20][23] the degree of nasal obstruction, based on rhinomanometry test values, was estimated as fraction of predicted values (p.v.) of rhinomanometric parameters:

- grade 1 corresponded to no obstruction (71-100% of p.v.);
- grade 2 to mild obstruction (57-70% of p.v.);
- grade 3 to moderate obstruction (43-56% of p.v.);
- grade 4 to severe obstruction (29-42% of p.v.) and
- grade 5 to very severe obstruction (less than 29% of p.v.)

Nasal mucociliary transport time (MCTt) was calculated by placing a tracer powder (charcoal) on the head of the inferior turbinate. The path of the powder was followed by direct pha-

Tab. II. Standard prick test panel for inhalant allergens.

STANDARD PRICK TEST PANEL FOR INHALANT ALLERGENS	
HISTAMINE HYDROCHLORIDE 0,1% (POSITIVE CONTROL)	
NACI 0.9% (NEGATIVE CONTROL)	
Hazel	<i>Corylus avellana</i>
Alder	<i>Alnusincana</i>
Birch	<i>Betula alba</i>
Plane	<i>Platanusvulgaris</i>
Cypress	<i>Cupressussempervirens</i>
Grass mix	smooth meadow grass (<i>Poa pratensis</i>), cock's foot grass (<i>Dactylis glomerata</i>), perennial rye grass (<i>Lolium perenne</i>), timothy grass (<i>Phleum pratense</i>), meadow fescue (<i>Festuca pratensis</i>), meadow oat grass (<i>Helictotrichon pretense</i>)
Olive	<i>Olea europaea</i>
Mugwort	<i>Artemisia vulgaris</i>
Ragweed	<i>Ambrosia artemisiifolia</i>
<i>Alternaria</i>	<i>Alternaria alternata (tenuis)</i>
<i>Cladosporium</i>	<i>Cladosporium herbarum</i>
<i>Aspergillus</i>	<i>Aspergillus fumigatus</i>
<i>Parietaria</i>	<i>Parietaria</i>
Cat	
Dog	
<i>Dermatophagoides pteronyssinus</i>	
<i>Dermatophagoides farinae</i>	
Blatella	<i>Blattella germanica</i>

Tab. III. Onset of headache attack

ONSET OF HEADACHE ATTACK	ALLERGIC (CASES)	NON-ALLERGIC (CONTROLS)	TOTAL
At morning	48	3	51 (53,1%)
At afternoon	10	3	13 (13,6%)
At evening	2	20	22 (22,9%)
During the night	7	3	10 (10,4%)
Total	67	29	96

ryngoscopy on the posterior wall of the pharynx. The charcoal powder is an inert non soluble tracer which is trapped in the gel layer of the mucus and is transported passively by the movement of the cilia [22] [24]. Transport time was calculated as the average of the values obtained from the two nasal fossae.

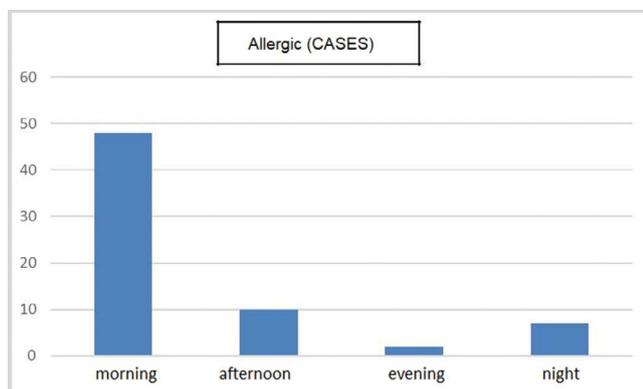


Fig. 1. Migraine onset during the day in allergic patients.

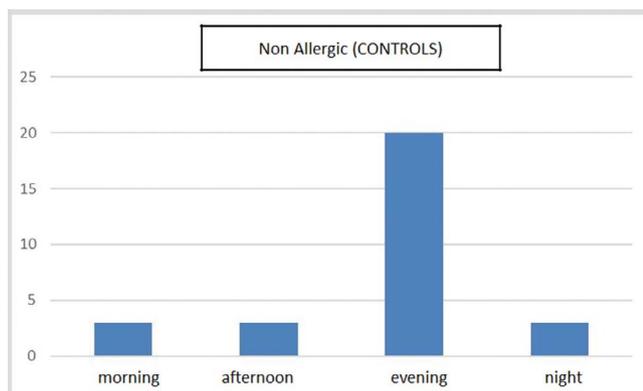


Fig. 2. Migraine onset during the day in non-allergic patients.

Moreover, parents were instructed not to use medications to their children at least 12 hours before the test.

RESULTS

Headache

Out of 800 children screened, only 96 (12%) suffered from headache. Among those little patients, 67 of resulted to suffered from both headache and allergies (case study group), while 29 were cephalalgic only (control group).

We analyzed main clinical features of cephalalgic symptoms in our population and then we compared a few characteristics of the headache between the two groups.

We initially analyzed the dependence of allergic and non-allergic groups with the occurrence of headaches during the day in the two groups (Tab. III.).

Tab. IV. The correlation and P value between allergic / non-allergic and phases of the day.

	MORNING	AFTERNOON	EVENING	NIGHT
Presence of allergy	0,56401	0,06147	-0,72082	0,00155
P value	<,0001	0,5519	<,0001	0,9881

Tab. V. Average duration of headache attack

AVERAGE DURATION OF ATTACK	ALLERGIC (CASES)	NON ALLERGIC (CONTROLS)	TOTAL
About 1 hour	25	9	34 (35,4%)
2-6 hours	20	12	32 (33,3%)
More than 6 hours	22	8	30 (31,3%)
Total	67	29	96

Tab. VI. Frequency of the cephalalgia

FREQUENCY OF CEPHALALGY	ALLERGIC (CASES)	NON ALLERGIC (CONTROLS)	TOTAL
More than twice a month	23	9	32 (33,3%)
Once or twice a month	33	14	47 (49%)
Less than once a month	11	6	17 (17,7%)
Total	67	29	96

Tab. VII. Localization of headache

LOCATION OF CEPHALALGY	ALLERGIC (CASES)	NON ALLERGIC (CONTROLS)	TOTAL
Frontal head region	54	25	79 (82,3%)
Parietal head region	6	2	8 (8,3%)
Diffused	7	2	9 (9,4%)
Total	67	29	96

Tab. VIII. Familiarity for headache

FAMILIARITY FOR HEADACHE	NUMBER OF PATIENTS (CASES + CONTROLS)
Maternal	23 (24%)
Paternal	14 (14,5%)
Both	2 (2%)
No familiarity	57 (59,5%)

As a measure of independence, we used the Cramer V, which ranges from 0 to 1. The value of this measure was 0.743563 which indicates a clear dependence between allergy and occurrence of the headache in the different periods of the day.

Then We used Pearson's correlation index to see if there was a

relationship between the allergic condition and the occurrence of the headache in each individual phase of the day.

We found that there was a significant and positive correlation (0.56401) between allergy and headache onset in the morning, while those who did not suffer from allergy have showed a significant correlation with the occurrence of headache in the evening hours (-0.72082). In the afternoon and at night the correlation was practically nil. Tab. IV. shows the correlation and Pvalue between allergic / non-allergic and phases of the day.

To calculate the correlations we used the variable "Presence of allergy" which is 1 in the case of allergy and 0 for non-allergy. The phases of the day are also represented by 4 dichotomous variables that are worth 1 in case of the occurrence of the headache (for each phase of the day) and 0 in the absence of headache.

The average duration of headache attack was variable in each group (Tab. V.). In fact, even if among allergic patients (case study group) the headache attack lasted for about one hour in the majority of cases, and in non-allergic group (controls) the average duration of the headache attack ranged usually between 2 and 6 hours, the correlation was -0.00580 with a P value (0.9553) close to zero. We can conclude that these parameters are independent and there isn't any relationship between presence/absence of allergy and duration of the migraine.

The correlation was calculated between the variable „Presence of allergy" and the polytomous variable „Duration" (its value was 1 in case of one-hour duration, 2 in case of 2-6 hours and 3 in case of more than 6 hours).

As regards the frequency of the cephalalgic attacks (Tab. VI.), we observed that there were no significant differences between allergic and non-allergic patients; in fact, in the majority of cases, headache occurred once or twice a month in both groups (49%).

In our sample (Tab. VII.) the cephalalgic pain was mostly localized in the frontal region (79 children, 82.3%) and only 9 patients (9.4%) suffered from diffused headache.

Thirty-nine children (40.6%) had a positive familiar anamnesis history for cephalalgia (Tab. VIII.): a maternal predisposition was found in 23 patients (24%), paternal in 14 patients (14.5%); only 2 little patients had both parents suffering from headache. The remaining 59.5% (57 children) could not indicate a familiar predisposition to migraine attacks.

Through the Pearson correlation we analyzed the relationship

Tab. IX. Presence of prodromal symptoms.

PRESENCE OF PRODROMAL SYMPTOMS	ALLERGIC (CASES)	NON ALLERGIC (CONTROLS)	TOTAL
Yes	6	9	15 (15,6%)
No	61	20	81 (84,4%)
Total	67	29	96

Tab. X. Prodromal symptoms connected with headache.

PRODROMAL SYMPTOMS	NUMBER OF PATIENTS (CASES + CONTROLS)
Aura/sparkling scotomas	3
Visual impairment	1
Nausea/vomiting	13
Dizziness	3

Tab. XI. Gender.

	< 13 YEARS	> 13 YEARS	TOTAL
Female	20	34	54 (56,2%)
Male	26	16	42 (43,8%)
Total	46	50	96

Tab. XII. Drug used during or before the headache.

DRUG USED DURING OR BEFORE THE HEADACHE	ALLERGIC (CASES)	NON-ALLERGIC (CONTROLS)	TOTAL
Paracetamol/FANS	17	13	30 (31,3%)
Other	27	5	32 (33,3%)
Nothing	23	11	34 (35,4%)
Total	67	29	96

Tab. XIII. Rhinomanometric values at 150 Pa (Pa/mmC)

RHINOMANOMETRIC VALUES AT 150 PA (PA/MMC)	NUMBER OF PATIENTS	ZAPLETAL CLASSIFICATION
< 0.5	29 (30,2%)	stopień 1
0.5–0.7	32 (33,3%)	stopień 2
0.7–1	28 (29,2%)	stopień 3
>1	7 (7,3%)	stopień 4–5

between allergic/non-allergic patients and the presence of prodromal symptoms of migraine (Tab. IX.). The two variables (presence of allergy and presence of migraine) have a correlation of - 0.27921 (P value 0.0059), so we can say that there is a correlation between non-allergic subjects and the presence of prodromal symptoms.

Prodromal symptoms connected with headache were repor-

ted to be (Tab.10) dizziness, aurea, sparkling scotomas, nausea and vomiting. No prodromal symptoms were reported by the vast majority of patients (81, 84.4% of our population). Only 15 patients (15.6%) reported the presence of neurovegetative and/or visual symptoms before or during the cephalalgic attack: the most frequent prodromal symptoms were nausea and vomiting (13 patients), while dizziness, visual impairment, aurea and scotomas occurred in 7 patients only.

Using the same above mentioned statistical analysis, we studied the relationship between the age of the patients and gender. We noticed that (Tab. XI.) there was a correlation between the variable gender (1 for females and 0 for males) and age of the patient (1 in case of younger children and 0 if they were over older than 13) is equal to -0.24694 with a P value of 0.0153.

Finally, we investigate the therapy that the little patients implemented in case of migraine. In 34 of 96 cases (35.4%) no specific therapy was administered. 30 patients took Paracetamol or FANs during the attack, while 32 patients (40%) were already taking antihistaminic therapy and/or nasal topical spray Narivent [Composition: mannitol, glycerol, glicirrizinatedipotassium, PEG/PPG copolymer, sodium EDTA, sodium N-(hydroxy-methyl)glicinate, polysorbate 20, potassium sorbate, sodium hydrate, purified water, natural aromas] when the pain attack occurred. Among the allergic patients the most utilized therapy during or before the headache attack was antihistaminic and/or nasal topical spray, while in non-allergic patients Paracetamol or FANS were used in the majority of cases.

3.2 Allergic rhinitis

According to international criteria [11] we subjected our population to prick testing: 67 out of 96 patients (69.8%) had a positive cutireaction to one or more of the tested allergens.

The whole population (both allergic and non-allergic cephalalgic children) underwent anterior rhinoscopy. We found rhinoscopic signs of allergic rhinitis in 67 patients: pale mucous membrane, inferior turbinates hypertrophy, aqueous nasal discharge. Instead in the other 30.2% (29 patients) no signs of allergic rhinitis were observed and the anterior rhinoscopy findings were within the normality range.

Nasal endoscopy confirmed the presence of allergic rhinitis objective symptoms found in anterior rhinoscopy in all the 67 patients: pallor and dystrophy of the septal mucous membrane associated with turbinates hypertrophy and serous nasal discharge were constant findings among these patients (69.8%). No evidence of rhino-sinusitis was found.

Manual rhinomanometry (Tab. XIII.) performed within the whole population with the foregoing [18] [19] [20], showed that in the very same 67 patients whose prick tests have been positive, nasal pressure values exceeded the threshold set at 0.5 Pa/mmc at 150 Pascal pressure. Twenty-nine out of 96 patients (30.2%) had nasal pressure values lower than 0.5 Pa/mmc, so they could be classified "grade 1- no obstruction" in accordance with Zapletal classification. In 32 patients (33.3%) there was a mild obstruction of nasal air flow (grade 2) with pressure values between 0.5 and 0.7 Pa/mmc; while in 28 children (29,2%) a moderate obstruction was found (grade 3, pressure values between 0.7 and 1 Pa/mmc). Finally, only 7 cases (7.3%) had a severe nasal obstruction (grade 4-5 of Zapletal classification) with rhinomanometric nasal pressure upper than 1 Pa/mmc.

Mucociliary transport time test with placing a tracer powder (charcoal) was performing referring to previous studies [22] [24]. Among the mentioned 67 allergic patients we found an impairment of the mucociliary function in the nose, while in non-allergic patients (29) there weren't any alterations, as similarly to normal children, who have shown an MCTt value of 11 minutes (± 3) for charcoal [25].

4. DISCUSSION

The prevalence of cephalalgic migraine in our sample is 12%, which remains in accordance with international works literature that estimates the prevalence of migraine to be between 3.3% and 21.4% in pediatric population [1] [2]. As regards the prevalence of allergic respiratory manifestations in our cephalalgic pediatric population, it was accounted for 69.8%, i.e. definitely higher than in international data; in fact according to the International Study on Asthma and Allergy in Childhood, the prevalence of allergy ranges from 8.1% to 10.5% among children aged between 6 and 14 years old. [4] [5]

In order to explain this high prevalence of allergic subjects among cephalalgic children we took into consideration the etiology and pathophysiology of both migraine and allergic rhinitis.

Currently, an integrated theory of migraine that involves both vascular and neuronal components is generally accepted. It has been demonstrated that the visual aura experienced by some migraine cephalalgic patients arises from cortical spreading depression, and this neuronal event can also activate perivascular nerve afferents, leading to vasodilatation and neurogenic inflammation of the meningeal blood vessels and, thus, throbbing pain. Also hypoxia induced by chronic respiratory obstruction, especially an hypoxic condition during sleep, can lead to vasodilatation of meningeal blood vessels as a response

to a continuous reduction in the haemoglobin oxygen saturation. Seasonal and perennial allergy can lead to reduction of nasal patency and, consequently, respiratory obstruction that can induce the cephalgic attack. During sleep, the hypoxic condition is more prolonged and severe than the daytime; in effect, in our sample, 51 patients (53.1%) referred that migrainous headache appears in the morning (Tab. III.).

In addition, the benefit of using medications like antihistaminic therapy and/or nasal topical spray (Narivent) during or before the migraine attack can be explained by the allergic nature of the headache.

Average duration of headache attacks was about one hour in most cases (34 patients, 35.4%) in accordance with international studies and guidelines that analyze migraneous and non-migraneous headache features in children. [29] [30]

The frequency of migrainous cephalgic attacks occurs once or twice a month in most cases (47 children, 49% of patients), both among allergic and non-allergic patients. This data, in line with international literature [5] [26], is representative of the social impact and discomfort caused by repeated headache attacks on the daily lives of children and adolescents and their families.

In accordance with international works [27] [28] [29], our sample reported that the migraneous pain was localized in the frontal head region in the vast majority of cases in both groups (79 children, 82.3%); this finding could be explained, for the allergic patients, by the nasal airflow impairment. In our sample (Tab.7) the cephalgic pain was mostly localized in the frontal region (79 children, 82.3%) and only 9 patients (9.4%) suffered from diffused headache.

Familiarity for headache was not a constant finding in our sample, and only 39 children (40.6%) had a positive familiar anamnesis for cephalalgia while the remaining 57 children (59.5%) couldn't indicate a maternal or paternal predisposition to migraine attacks. These data, that aren't in accordance with many clinical studies [25] [30] that report a positive familiar anamnesis for migraneous headache in about 70% of cases, suggest a different origin of cephalgic pain attack, or rather headache caused by hypoxia, such allergic nasal obstruction.

Also prodromal symptoms are inconstant findings, in fact only 15 patients (15.6%) referred the presence of neurovegetative symptoms before or during the cephalalgia; contrariwise in 81 children (84.4% of our sample) headache pain attacks occur without prodromal symptoms. Several international studies [32] [33] report the prevalence of prodromal symptoms in children

range from 66.9% to 73.9%. Therefore, this modest discordance of prevalence in our sample lies in favor of the allergic nature of migraine. Moreover, the statistical analysis performed through Paerson correlation show that there is a correlation between non-allergic subjects and the risk of prodromal symptoms. This can be explained by the different etiology of the attack of migraine, inflammatory in the case of non-allergic and hypoxic subjects in the case of allergic subjects.

In accordance with international studies [34] [35] also in our sample there is no statistically significant difference between male and female sex in children under the age of 13, while adolescents (between the ages of 13 and 19 years old) migraine headache affected females more frequently than males.

According with previous studies [35] among the 67 allergic patients we found an impairment of the mucociliary function in the nose, while in non-allergic patients there weren't any alterations as in normal children, who have a MCTt value of 11 minutes (± 3) for charcoal.

To conclude, as suggested by our data, we found that there is a strong relation between headache and allergic rhinitis in children. Thus, for an effective diagnostic and therapeutic approach to migraine, the pediatrician should take into account atopy and its related allergic manifestations. Therefore, not only should the pediatrician investigate cephalgic common triggers, but sneezing, asthma, atopy familiarity, nasal discharge, nasal patency as well, requesting also an otorhinolaryngologist or allergologist consult if necessary.

These findings also stress the potential role of drugs that are not usually utilized for migraine attacks, such as antihistaminic or topical nasal decongestant sprays. While paracetamol has a good analgesic effect, a targeted therapy using antihistaminic drugs could reduce onset of headache attacks and could prolong the period of well-being between consecutive attacks.

Moreover, children with migraine have an increased risk of school performance impairment, as factors associated with this impairment have already been identified

Future studies should address the directionality of the association and putative mechanisms to explain it.

Acknowledgements

Nothing to declare

Funding surces

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Word count: 2900 Tables:13 Figures: 2 References: 36

Access the article online: DOI: 10.5604/01.3001.0011.7252 Table of content: <https://otolaryngologypl.com/issue/11198>

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Competing interests: The authors declare that they have no competing interests.

Cite this article as: Passali F, A., Spinosi M., C., Mignacco G., Cingi C., Rodriguez H., A., Passali D.; Influence of allergic rhinitis in children and adolescents with recurrent headache. *Otolaryngol Pol* 2018; 72 (2): 48-57
