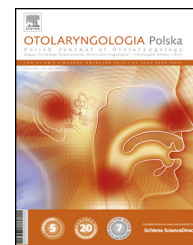


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Original research article/Artykuł oryginalny

Role of immunoglobulin E and gastro-esophageal reflux disease in the development of otitis media with effusion



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ABSTRACT

Introduction: The role of allergy in chronic otitis media with effusion (OME) is controversial. **Aim of the work:** To study the role of allergy and gastroesophageal reflux diseases in the etiology of OME. **Materials and methods:** It is a prospective study that was done on 43 cases; 30 patients suffer from OME with mean age 6.8 years and 13 control child with mean age 8.3 years. Blood sample were taken from patients and control children for assay of total Immunoglobulin E (IgE) and serum pepsinogen 1 (PG1). Effusion fluid samples were taken from middle ear of the patients during myringotomy and ventilation tube insertion; IgE and PG1 were assayed in the effusion samples. Total IgE and PG1 were assayed by enzyme-linked immunosorbent assay. **Results:** Our results showed that, there is a correlation between serum IgE and Effusion IgE in the patients group, there is a significant negative correlation between PG1 in the effusion and serum of the studied patients. **Conclusion:** Allergy is a possible risk factor for the development of OME. The level of PG1 in the effusion is one tenth of its level in the serum of the patients.

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Introduction

Otitis media with effusion (OME) is defined as chronic inflammation of the middle ear mucosa characterized by the retention of fluid behind an intact tympanic membrane (TM) within the middle ear space without signs or symptoms of an acute ear infection [1–3]. The most common complication of OME is hearing loss, and it is the commonest cause of hearing loss in children [4]. Allergy and otitis media (OM) are both very common conditions and are

linked epidemiologically and mechanistically [5]. Only recently oesophago-laryngo-pharyngeal reflux has been taken into consideration as a possible risk factor for Eustachian tube dysfunction [6].

Patients and methods

The studied population includes 43 individuals, patients and controls were selected from ENT department, Minia university hospital in the period from March 2011 to October 2011.

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The study sample was divided into 2 groups:-

Group I (cases): It includes 30 diseased children with OME (resistant to medical treatment or recurrent after successful medical treatment). Patients were subjected to myringotomy with insertion of tympanostomy tube (Grommet or T-tube). Their age ranged from 1.5 to 15 years (14 males and 16 females).

Group II (control): It includes 13 diseased children with ENT disease other than OME mostly adenoidal or tonsillar hypertrophy. Their age ranged from 3 to 14 years (6 males and 7 females)

Exclusion criteria

1. Acute otitis media.
2. Perforated tympanic membrane.
3. Sensorineural hearing loss.
4. Immunodeficiency diseases.
5. Down's disease.
6. Cleft palate.
7. Patients with gastric problems.
8. Craniofacial abnormalities.
9. Chronic underlying medical disease.

Each group was subjected to:

- (1) Careful history taking, including history suggesting allergy – such as symptoms suggesting allergic rhinitis, asthma, eczema, urticaria, conjunctivitis, food sensitivity and anaphylaxis – or history suggesting GERD such as heart burn,
- (2) General examination,
- (3) Clinical otorhinolaryngologic examination,
- (4) Audiological evaluation in the form of pure tone audiometry and tympanometry,
- (5) Effusion fluid sample obtained from patients by wide bore syringe during myringotomy and tympanostomy tube insertion under complete aseptic conditions, middle ear effusion obtained from one or both ears of the same case was considered a single sample; assay of Immunoglobulin E (IgE) and pepsinogen I by ELISA,
- (6) Blood sample obtained by Sterile venipuncture from both patients and control subjects for Assay of serum total IgE and pepsinogen I by ELISA.

IgE kits supplied by D.S. I. Italy and PG1 kit supplied by D.R. G. International, Inc., USA.

Results

The current study is a prospective study, that was done between March and October 2011, at Otorhinolaryngology department, Minia University Hospital. The study was approved by the research Ethics committee of Minia University and written informed consent was signed by parents of enrolled children.

The study was done on thirty patients who suffer from OME and 13 control subjects. The age range of the patients was 18 months to 15 years, with mean age 6.8 years. The gender of patients was 16 females and 14 males (Tab. I). The control sample had 6 males and 7 females who did not

Table I – Sex distributions for patient's group

Sex	No.	%
Male	14	46.5
Female	16	53.5
Total	30	100%

suffer from OME; the mean age was 8.3 years, as shown in Table II.

Regarding IgE, the IgE in the serum of the patients was 40–932.11 IU/mL with mean value 315 IU/mL. While IgE in the serum of control samples was 55–400 IU/mL with mean value 153.5 IU/mL. Our results showed that, IgE is higher in the serum of the patients than in control subjects, and there is a significant correlation between IgE in the serum of patients and that of control cases as $P = 0.05$, while serum PG1 in both groups did not correlate as shown in Table III.

As regard of pepsinogen 1 (PG1), our results showed that its level in the serum of the patients was 20.1–245.2 ng/mL. With mean value 89.5 ng/mL, while in the control group, it ranged from 5 ng/mL to 248.1 ng/mL with mean value 97 ng/mL. The level of PG1 in the effusion of the studied patients was 5–18 ng/mL with mean value 9.2 ng/mL.

The study revealed that there is a correlation between total serum IgE and effusion IgE in patient's group as $P = 0.00$, while Serum PG1 correlates with effusion PG1 as $P = 0.00$. Our data also showed that serum total IgE correlates with serum PG1 and effusion PG1 as $P = 0.00$, also there is a correlation between effusion total IgE and effusion PG1 as shown in Table IV.

Discussion

The study was done to shed a spot of light on the role of allergy and gastroesophageal reflux on the etiology of secretory otitis media.

OME is known as the presence of fluid in the middle ear without signs or symptoms of acute middle ear infection. The persistence of the middle ear effusion (MEE) for at least 3 months is defined as chronic otitis media with effusion (COME). It is a multifactorial disease and still remains as the most common cause of deafness in children. The causes of COME include eustachian tube dysfunction, upper respiratory tract infection, insufficient aeration of the mastoid cells, mucociliary clearance abnormalities, adenoid disease, allergic rhinitis, and immunologic disorders. Gastroesophageal reflux (GER) has also been implicated as a possible associated factor in the pathogenesis of COME. It has been demonstrated that pepsin and pepsinogen were present in the MEE of patients with COME [7]. The role of allergy in COME is controversial [8].

Table II – Sex distributions for control group

Sex	No.	%
Male	6	46.5
Female	8	53.5
Total	13	100%

Table III – Comparison between serum total IgE and serum pepsinogen 1 in two groups

	Mean $\pm$ SD		P-value
	Group I	Group II	
Serum Total IgE	313.03 $\pm$ 282.67	153.46 $\pm$ 107.80	0.05*
Serum Pepsinogen 1	88.09 $\pm$ 55.50	97.00 $\pm$ 68.42	0.65**

* Significant.

** Non-Significant.

Our study was done using 43 cases, 30 patients with secretory otitis media with mean age 6.8 years and 13 control children with mean age 8.3 years. Serum level of total IgE and PG1 was assayed in patients and control groups as well as in the effusion of patients group.

Our data showed that, the IgE in the serum of the patients was 40–932.11 IU/mL with mean value 315 IU/mL. While IgE in the serum of control sample was 55–400 IU/mL with mean value 153 IU/mL. The total IgE level in normal, (allergy-free adults) is less than 190 IU/mL in the serum. This means that, there is evidence of allergic etiology in patients who suffer from secretory otitis media, as our results showed that, there is a correlation between serum total IgE and effusion IgE in the patients group as $P = 0.02$, also the serum level of total IgE is higher in the serum of patient's group than control group.

Amirzargar et al. [9] showed that the serum IgE concentration of normal individuals is 10–100 IU/ml. Arroyave et al. demonstrated the association between recurrent otitis media with effusion and food allergy [10]. Our results showed that, IgE is higher in the serum of the patients than in control subjects, and there is a significant correlation between IgE in the serum of patients and that of control cases as $P = 0.05$.

The significant incidence of atopy associated with otitis media with effusion has suggested a role of allergy in the pathogenesis of OME. Analysis of inflammatory mediators indicates that the mucosa of the middle ear can respond to antigen in the same way as does the mucosa of the lower

respiratory tract. Recent characterization of the mucosa and effusion from atopic patients with OME reveals a T helper 2 (Th2) cytokine and cellular profiles consistent with an allergic response, supporting the role of allergy in OME. In addition, animal studies demonstrate that inhibiting characteristic allergy cytokines can prevent the production of middle ear effusion. As the understanding of allergy and its role in the inflammation of OME continues to deepen, this will introduce focused treatments of OME in the atopic population [11].

Keleş et al. [12] showed in their study that IgE level was significantly higher in the serum samples of the patient group when compared with those of the control group. These results are in agreement with our results.

The results of Alles on 2001 agree with our results as he concluded that allergy was more common in a group of children with chronic or recurrent otitis media when compared with the general population [13]. Localized specific immunoglobulin E production in the middle ear fluid can be detected from children with OME [14].

Our results disagree with the conclusion of Skoner et al. [15] who stated that, there is causal relationship between allergy and otitis media conditions, but conclusive proof is lacking. Allergic rhinitis and adenoiditis are significant risk factors to OME development and that the risk becomes higher when these two conditions are con-comitantly present [16]. Low expression of CD80 and CD86 indicates that local immunity response in hypertrophied adenoids in children with otitis media with effusion is weakened. It can contribute to the otitis media with effusion [17].

Chantzi et al. [2] demonstrated that OME is independently associated with IgE sensitization, symptoms of respiratory allergy, and otitis heritability. Additionally, they are suggestive of an interaction of allergy and viral infections in the upper airways, leading to an increased risk of OME development. Among the above factors, symptoms of respiratory allergy are the most straightforward targets for possible intervention; the effectiveness of relevant medications in preventing and/or treating OME should now be scrutinized. Analysis of the effusion content have consistently revealed significantly elevated levels of allergy-related mediators (IL-4, IL-5, IL-6, RANTES, ECP, tryptase, IgE) as well as differences between atopic and nonatopic patients with OME [18]. Our results agree with this report as IgE is elevated in all cases of patient's group compared to control group.

Our results showed that, the mean level of PG1 in the serum of the patients is 89.5 ng/ml, while in the control group the mean value is 97 ng/ml. PG1 was present in the effusion of all cases of secretory otitis media, the level of

Table IV – Comparison between serum total IgE and effusion total IgE, serum pepsinogen1, effusion pepsinogen 1 in group I (n = 30)

	Mean $\pm$ SD	P-value
Serum total IgE	313.03 $\pm$ 282.67	
Effusion total IgE	98.33 $\pm$ 48.73	0.000*
Serum total IgE	313.03 $\pm$ 282.67	
Serum pepsinogen 1	88.09 $\pm$ 55.50	0.000*
Serum total IgE	313.03 $\pm$ 282.67	
Effusion pepsinogen 1	9.16 $\pm$ 3.86	0.000*
Effusion total IgE	98.33 $\pm$ 48.73	
Serum pepsinogen 1	88.09 $\pm$ 55.50	0.46**
Effusion total IgE	98.33 $\pm$ 48.73	
Effusion pepsinogen 1	9.16 $\pm$ 3.86	0.000*
Serum pepsinogen 1	88.09 $\pm$ 55.50	
Effusion pepsinogen 1	9.16 $\pm$ 3.86	0.000*

* Significant.

** Not significant.

PG1 in the effusion of the studied patients was 5–18 ng/ml with mean value 9.2 ng/ml.

Al-Saab et al. [3] stated that, the presence of pepsinogen was detected in 84% of middle ear effusion from the OME group, at concentrations 1.86–12.5 times higher than that of serum. Our results disagree with Al-Saab as we found that PG1 is present in 100% of effusion and the concentration of it in the effusion was one tenth of its concentration in the serum.

Our results disagree also with Tasker et al., as they found that, the concentrations of pepsin and pepsinogen that recorded in the effusions were around 1000 times higher than those found in serum [19].

Other confirmed finding in children and adults with OME showed the specificity of the plasma ELISA test for pepsinogen in the middle ear effusions remains unknown, so the observed rates of pepsinogen varies [20] and the increased pepsinogen contents were not necessary related to any increased GER symptoms [21].

The presence of pepsinogen in the middle ear effusion supports the relation between gastroesophageal reflux and otitis media with effusion. Measurement of pepsin/pepsinogen can be considered as a simple and reliable method for assessment of reflux in children. However, further research is needed to establish a definite association between GER and OME before beginning antireflux treatment in the management of OME. Measurable pepsinogen was present in all MEEs from patients, with levels higher than the serum values. The difference between the levels of pepsinogen measured in MEE and serum was statistically significant [22].

Pepsin is detectable in the middle cleft of 20% of pediatric patients with otitis media (OM) undergoing tympanostomy tube placement, compared with 1.4% of controls; recovery of pepsin in the middle ear space of pediatric patients with OM is an independent risk factor for OM [23].

Measurement of PGI in the middle ear effusions can be used to screen for the existence of GER [24], and it was significantly more frequent than allergy in patients with otitis media [25]. Our results disagree with these reports and we assume that PG1 present in the effusion of the patient, is a transudation from the serum and is not due to actual reflux through Eustachian tube.

Children with otitis media with effusion or recurrent acute otitis media and GERD have improved quality of life following treatment with antireflux therapy. Control of gastroesophageal reflux may play a role in the management of otitis media and avoidance of tympanostomy [26]. In children with associated laryngo-pharyngeal reflux, is related to the contact of the refluxate with the rhinopharyngeal areas and, consequently, with the pharyngeal orifice of the Eustachian tube [3]. Repeated exposure of the ciliated epithelium of the respiratory tract to a PH of 4 or less, inevitably leads to stasis of the latter. In turn, this results in impaired mucociliary clearance. Furthermore, hydrochloric acid and pepsin induce local inflammation, mucosal edema and ulcerations in the mucosa of the respiratory tract; inflammation of the Eustachian tube, in particular, causes an obstruction which, in turn, leads to loss of ventilatory

function. This damage triggers a series of events leading to an objective otoscopic pattern of otitis media [27].

The prevalence of gastroesophageal reflux disease in children with chronic otitis media with effusion/recurrent acute otitis media may be higher than the overall prevalence for children. Presence of pepsin/pepsinogen in the middle ear could be related to physiologic reflux. A cause-effect relationship between pepsin/pepsinogen in the middle ear and otitis media is unclear. Antireflux therapy for otitis media cannot be endorsed based on existing research [28].

Conclusion

1. Total IGE is higher in the serum of patients with OME, than the serum of control group.
2. There is positive significant correlation between IGE in the serum and that in the effusion of patients with OME.
3. The level of PG1 in the effusion is one tenth its level in the serum of the patients
4. There is no correlation between IGE and PG1 in the effusion of the patients.

Authors' contributions/Wkład autorów

MAG – idea of the paper, diagnosis of the patients, collection of effusion samples, writing and editing of the paper. ARAAK – collection of the effusion samples, share in writing of the paper. YME – assay of IgE and PG1 in the blood and effusion.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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