

PRESCENCE OF GASTRIC PEPSINOGEN IN THE MIDDLE EAR FLUID OF PATIENTS WITH OTITIS MEDIA WITH EFFUSION

By

Abd El-Rahman Mohamad Abou Bakr Abou Halfa, Ali Abdallah Abd El-Rahman, Tarek Mustafa Emran and Mohammad Fatehy Ramadan

Department of Otorhinolaryngology Faculty of Medicine, Al-Azhar University, EGYPT

E-mail: abderahmanabohalfa2016@gmail.com

ABSTRACT

Background: Gastroesophageal reflux (GERD), in particular extra-esophageal reflux, has been associated with a variety of upper aerodigestive tract symptoms or diseases such as sinusitis and otitis. Many studies showed the role of reflux in chronic otitis media with effusion in children.

Objective: To investigate the relationship between gastro-esophageal reflux diseases (GERD) and otitis media with effusion (OME) by evaluation of the presence of gastric pepsinogen in middle ear fluid of patients with OME.

Patients and methods: Prospective study was conducted on 24 patients. Those patients suffered from recurrent otitis media with effusion, undergoing bilateral myringotomy with ventilation tube insertion and middle ear effusions, as well as blood samples were collected. All cases were subjected to history taking and ENT examination. Total pepsinogen concentrations of effusions and serum samples were measured with an enzyme-linked immuno sorbent assay (ELISA) using Human Pepsinogen I ELISA Kit (CUSABIO, USA).

Results: The mean age of the included cases were 32.7 years. Patients were 25 females (62.5%) and 15 males (37.5%). The mean value of GERD score was 11.18 (range, 10 – 12). The four tympanogram types did not differ in age and gender. All the cases with type B and C tympanometry in the right ear was with GERD score of 11 and 12.

Conclusion: GERD is considered as one of the contributing factors in the etiopathogenesis of middle ear effusion.

Keywords: Otitis media with effusion, Gastroesophageal reflux disease, pepsinogen.

INTRODUCTION

Otitis media with effusion (OME) in all its manifestations is a worldwide major health problem for both of children and adults who have a lifelong history of eustachian tube dysfunction. Chronic otitis media with effusion (OME) is frequently encountered by otolaryngologists and is defined as middle ear effusion in one or both ears for 6 weeks to 6 months. OME is an

inflammatory condition of the middle ear mucosa, with sterile fluid collection in the middle ear space. It is highly prevalent during childhood, with more than 50% of children experiencing OME in the first year of life. Although most episodes resolve spontaneously, 5 to 10% of cases will persist for over 1 year (*Abd-Elhamid et al, 2012*).

Otitis media with effusion (OME) is associated with many factors, including

adenoid hypertrophy, upper respiratory tract infection, cleft palate, and exposure to cigarette smoke. In adults, OME is less prevalent, but still causes considerable morbidity. While adult OME was once a neglected subject in terms of research effort, this is no longer the case. Over the last 20 years, a great deal of new information that sheds some light on the pathogenesis of this enigmatic condition has become available (*Mills and Hathorn, 2016*).

The possible aetiologies and risk factor of adult OME are local malignancy, sinonasal disease, gastroesophageal reflux, eustachian tube dysfunction, smoking, intensive care patients, human immunodeficiency virus (HIV), and sarcoidosis (*Mills and Hathorn 2016*). Other common cause is allergy, which was reported in 41, 9% of cases (*Roozbahany et al., 2016*).

GER disease (GERD) occurs when gastric contents reflux into the esophagus or oropharynx and produce symptoms. It has been linked to the development of many airway disorders: croup, chronic cough, laryngospasm, laryngomalacia, vocal cord nodules, asthma, reactive broncho constriction, apnea, sudden infant death syndrome, rhinitis, sinusitis, subglottic stenosis, and glottic granuloma (*Toros et al., 2010*).

The possible relationship between GER and OME has been studied over recent years. GER is thought to cause inflammation of the nasopharynx, dysfunction of the Eustachian tube, and impairment of the mucociliary clearance, thus increasing in the incidence of OME. The repeated exposure of the ciliated respiratory epithelium to pH 4 or less

blocks ciliary movement and mucus clearance, HCl and pepsin cause local inflammation, edema, and ulceration of the respiratory mucosa, leading to loss of tube ventilatory function and this leads to impaired pressure equalization with persistent negative pressure, resulting in middle ear effusions (*Abdelshafy et al., 2015*).

The present work aimed to investigate the relationship between gastro-esophageal reflux diseases (GERD) and otitis media with effusion (OME) by evaluation of the presence of gastric pepsinogen in middle ear fluid of patients with OME.

PATIENTS AND METHODS

This prospective study was designed to investigate the relationship between gastro-esophageal reflux diseases (GERD) and otitis media with effusion (OME) by evaluation of the presence of gastric pepsinogen in middle ear fluid of patients with OME. This study was conducted on 24 patients, those patients suffered from recurrent Otitis media with effusion and coming from the outpatient clinic of ENT Department of Al-Azhar University Hospital, Damietta, Egypt.

Inclusion criteria: The age of the patients ranged from 5 to 25 years, and all patients had pure tone and tympanometry evidence of otitis media with effusion.

Exclusion criteria: Patients who were unfit for general anesthesia and surgery, patients with sensorineural hearing loss.

The consents for the surgery were taken from adult patients and parents of the children after complete illustration of surgery procedures and complication.

The whole study design was approved by the ethics committee of the Faculty of Medicine, Al-Azhar University.

All cases in the study were subjected to complete history taking, general medical history and associated comorbidities, and clinical examination. All patients were subjected to tympanometry, anterior rhinoscopy and otoscopy.

Statistical analysis: Data were coded, computed then analyzed using IBM SPSS

(Statistical package for the social sciences) (Chicago, USA) version 24 for Windows to obtain qualitative data which were presented as frequency and percentage and were compared by Fisher Exact Test. Quantitative data were presented as Mean ± Standard deviation (SD), Median, and range. P-values < 0.05 were considered significant.

RESULTS

This study included 24 patients suffered from recurrent Otitis media with effusion. The mean age of the cases was 10.17 ± 4.43 years with range between 5

and 20 years. There were 11 males (45.8%) and 13 females (54.2%) (**Table 1**).

Table (1): Demographic data in the cases of the study

Items		Cases (n= 24)
Age (years)	Mean ± SD	10.17 ± 4.43
	Median (min-max)	9.5 (5-20)
Sex		
Males		11 (45.8%)
Females		13(54.2%)

Continuous data were expressed as mean ± SD and median (range)
Categorical data were expressed as Number (%)

The mean level of pepsinogen in the serum was 72.8 ± 9.69 ng/ml with range between 55.4 and 85.7 ng/ml. The mean level of pepsinogen in the middle ear fluid was 107.4 ± 34.98ng/ml with range between 57.1 and 180.1 ng/ml. According

the mean level of pepsinogen in the middle ear effusion, there were 9 cases (37.5%) with no GERD, and 15 cases (62.5%) with GERD regarding the level of the pepsinogen in the plasma in the same patient (**Table 2**).

Table (2): Serum and middle ear fluid level of pepsinogen in the cases of the study

Cases (n= 24)		
Variables	Mean ± SD	Median (Range)
Level of pepsinogen in the serum (ng/ml)	72.8 ± 9.69	73.95 (55.4-85.7)
Level of pepsinogen in the middle ear fluid (ng/ml)	107.4 ± 34.98	111.75 (57.1-180.1)
		Frequency Percent
Classification of cases according to Level of pepsinogen in the middle ear effusion		
< 90 ng/ml (No GERD)		9 37.5
≥ 90 ng/ml (GERD)		15 62.5

Continuous data were expressed as mean ± SD and median (range)
Categorical data were expressed as Number (%)

Five cases (20.8%) had clinical reflux for reflux (**Table 3**). and 4 cases (16.7%) received medication

Table (3): Presence of reflux in the cases of the study

Cases (n= 24)		
	Frequency	Percent
Clinical reflux		
No	19	79.2
Yes	5	20.8
Medication for reflux		
No	20	83.3
Yes	4	16.7

Categorical data were expressed as Number (%)

Fourteen cases had reflux score of 0, and 10 cases had reflux score more than (**Table 4**).

Table (4): Analysis of reflux score of the cases in the study

Score	Frequency	Percent (%)
0	14	58.3
1	2	8.3
2	4	16.7
3	1	4.2
5	1	4.2
7	1	4.2
9	1	4.2

Categorical data expressed as Number (%)

There was statically significant level of pepsinogen in the middle ear positive correlation between reflux score and classification of cases according to effusion (**Table 5**).

Table (5): Correlation between reflux score and Classification of cases according to Level of pepsinogen in the middle ear effusion

Items \ cases	< 90 ng/ml (No GERD) (n=9)		≥ 90 ng/ml (No GERD) (n=15)		P value
	N	%	N	%	
Reflux score 0	9	100	5	33.3	P< 0.002*
Reflux score more than 0	0	0	10	66.7	

P: probability, Categorical data were expressed as Number (%).

FET: Fisher's exact test.

DISCUSSION

OME is the most common cause of deafness in children, and the etiology of OME is largely considered to be multi factorial including infections, allergies,

eustachian tube dysfunction, adenoid hypertrophy, etc but there is an increasing interest in GERD as one of the major contributing factors to this condition (*Nair et al., 2012*).

In this work, we have investigated the relationship between gastro-esophageal reflux diseases (GERD) and otitis media with effusion (OME) by evaluating of the presence of gastric pepsinogen in middle ear fluid of patients with OME. Pepsinogen reaching the middle ear by laryngopharyngeal reflux (LPR) is the most likely source of pepsinogen in the middle ear. Serum and middle ear pepsinogen levels were evaluated in our study. The middle ear pepsinogen levels in our study were higher than those in the serum, supporting the notion that LPR plays a role in the pathogenesis of OME. Our finding about the patients that have higher pepsinogen level in the middle ear than serum was in agreement with *Nair et al.*, (2012) in a prospective trial study, as they found that 65.63% (21 of 32) of patients with OME had high pepsinogen levels in their middle ear effusion samples, higher than 90ng/ml (*Nair et al.*, 2012).

Other studies suggest that pepsinogen in the middle ear can originate from diffusion of pepsinogen from blood: examination of the pepsinogen, fibrinogen, and albumin levels in the serum and middle ear showed no significant differences between the serum and middle ear fibrinogen and albumin levels, but the middle ear pepsinogen level was 1000-fold higher than that in the serum (*Dogru et al.*, 2015). Additionally, *Nair et al.* (2012) showed that the middle ear pepsinogen level was 65-fold higher than that in the serum. The hypothesis of a vascular origin of middle ear pepsinogen was refuted.

Other studies suggested that pepsinogen in the middle ear can originate

from endogenous production of pepsinogen in the middle ear. They showed that enzyme activity can occur in cases of severe inflammation and chronic discharge. Production of pepsinogen in the middle ear is also possible. Pepsinogen iso-enzymes are found in the lung, pancreas, prostate, and some malignant tissues. No pepsinogen 1 mRNA was found in infected mastoid mucosa by RT-PCR, and no evidence of pepsinogen production by immunohistochemical methods in middle ear biopsy specimens. *Luo et al.* (2014) found that the expression levels of pepsinogen protein in adenoid samples in the OME group were significantly higher than those in the adenoid hypertrophy group. However, pepsinogen mRNA could not be detected in either group. These data suggest that the detected pepsinogen protein was not originally produced in adenoid samples, but likely originated from other processes, such as laryngopharyngeal reflux (LPR). Our study was in accordance with previous studies. Endogenous pepsinogen production is unlikely according to these studies (*Luo et al.*, 2014 and *Dogru et al.*, 2015).

Our study has several limitations, performing 24h continuous esophageal pH monitoring and obtaining pepsinogen from the gastric juice could provide more sound evidence to establish causality between OME and GER, but both are invasive procedures and were not considered in the current study. Another limitation is that pepsinogen concentration in the middle ear fluid compared with serum and not with gastric content because obtaining gastric content which was also an invasive procedure. Finally, we could obtain middle ear fluid from

both ears in only a small number of patients with bilateral OME and hence could not measure pepsinogen concentration separately.

CONCLUSION

GERD was considered as one of the contributing factors in the etiopathogenesis of middle ear effusion.

REFERENCES

1. **Abd-Elhamid I, Ibrahimeldsoky I, Mahmoud A, Abd-Elaziz A and Shams M (2012):** Effectiveness of intratympanic injection of long acting steroids and local steroid nasal spray in patients of OME resistant to conventional therapy, *AAMJ*,10(3), 318-332.
2. **Abdelshafy IA, Atalla AT, AbdELAziz AE, Shehata WM and Gendy OAE (2015):** Pepsinogen Assay as a Marker of Reflux in Children with Otitis Media with Effusion. *J Otolaryngol ENT Res.*, 3(10):15406.
3. **Dogru M, Kuran G, Haytoglu S, Dengiz R and Arikan OK (2015):** Role of laryngopharyngeal reflux in the pathogenesis of otitis media with effusion. *J Int Adv Otol.*, 11: 66-71.
4. **Luo HN, Yang QM, Sheng Y, Wang ZH, Zhang Q and Yan J (2014):** Role of pepsin and pepsinogen: linking laryngopharyngeal reflux with otitis media with effusion in children. *Laryngoscope*, 124:294-300.
5. **Mills R. and Hathorn I (2016):** Aetiology and pathology of otitis media with effusion in adult life,” *The Journal of Laryngology & Otology*, 130 (5): 418–424.
6. **Nair S, Kumar M and Nair P (2012):** Role of GERD in children with otitismedia with effusion. *Indian J Pediatr.*, 79(10):1328-1332.
7. **Roobahany NA, Majdinasab N, Oroei M and Nateghinia S (2016):** Adult Onset Otitis Media with Effusion: Prevalence and Etiology, *Journal of Hearing Science Otolaryngology*, 2(1): 7–9.
8. **Toros SZ, Toros AB, Ozel L, Çatal, Kınış V, Zorlu A, Habeşoglu TE, Naiboglu B and Egeli E (2010):** Investigation of gastric pepsinogen in middle ear fluid of children with glue ear. *Acta Otolaryngol.*, 130(11): 1220-1224.

وجود البيبسينوجين المعدي في سائل الأذن الوسطى في
المرضى الذين يعانون من إرتشاح الأذن الوسطى
عبد الرحمن محمد أبو حلفه، علي عبد الله عبد الرحمن، طارق مصطفى عمران،

محمد فتحي رمضان

قسم الأذن والأنف والحنجرة، كلية الطب، جامعة الأزهر

البريد الإلكتروني: abderahmanabohalfa2016@gmail.com

خلفية البحث: إرتبط الارتجاع المعدي المريئي، وخاصة الارتجاع خارج المريء، بمجموعة متنوعة من أعراض أو أمراض الجهاز الهضمي العلوي مثل التهاب الجيوب الأنفية و التهاب الأذن. وتُظهر العديد من الدراسات دور الارتجاع في التهاب وارتشاح الأذن الوسطى المزمن عند الأطفال.

الهدف من البحث: بحث العلاقة بين ارتجاع المريء والارتشاح المزمن للأذن الوسطى عن طريق فحص وجود البيبسينوجين المعدي في سائل الأذن الوسطى في المرضى الذين يعانون من إرتشاح الأذن الوسطى.

المرضى وطرق البحث: تم جمع سائل إرتشاح الأذن الوسطى وعينات الدم من 24 مريضاً يعانون من الإلتهاب المزمن للأذن الوسطى مع الإرتشاح، مع عمل شق للطلبة مع إدخال أنبوب التهوية، وتم قياس تركيزات البيبسينوجين المجمع من الارتشاح وعينات المصل باستخدام مقايصة ماصة مناعية مرتبطة بالإنزيم (ELISA) باستخدام مجموعة بيبسينوجين I ELISA البشرية، وتم تسجيل جميع الحالات والتاريخ المرضي و فحصاً بدنياً شاملاً وفحصاً كاملاً لأمراض الأذن والأنف والحنجرة. وتمت الموافقة على الدراسة من قبل اللجنة الأخلاقية المحلية.

نتائج البحث: كان متوسط مستوى البيبسينوجين في المصل 9.69 ± 72.8 نانوغرام/مل و يتراوح بين 55.4 و 85.7 نانوغرام/مل، بينما كان متوسط مستوى البيبسينوجين في سائل الأذن الوسطى 34.98 ± 107.4 نانوغرام/مل

مل مع مدى يتراوح بين 57.1 و180.1 نانوغرام/مل. حسب متوسط مستوى البيسينوجين في إرتشاح الأذن الوسطى، وكانت هناك 9 حالات (37.5%) بدون إرتجاع المريء، 15 حالة (62.5%) مصابة بالارتجاع المعدي المريئي، 5 حالات (20.8%) عانت من ارتجاع سريري، 4 حالات (16.7%) تلقت أدوية للارتجاع، 14 حالة كانت درجة ارتجاعها 0 علاوة على 10 حالات بها درجة ارتجاع أعلى من 1.

الإستنتاج: إرتجاع المريء أحد العوامل المسببه لارتشاح الأذن الوسطى حيث يصل البيسينوجين المعدي إلى الأذن الوسطى عن طريق البلعوم الأنفي وقناة استاكيوس.

الكلمات الدالة: إرتشاح الأذن الوسطى، إرتجاع المريء، بيسينوجين.

قبول للنشر 8 / 8 / 2021