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ROLE OF REFLUX IN THE ETIOLOGY OF OTITIS MEDIA WITH EFFUSION IN CHILDREN

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ABSTRACT

Background: Chronic secretory otitis media is a common disease in children, especially in developing countries. In these countries secretory otitis media may pass unnoticed for a long time and then develop slowly into a chronic condition. In spite of the common occurrence of secretory otitis media, its etiology and pathobiology are still largely unknown. Causes of this disorder are believed to be multifactorial, including viruses, allergy, bacteria and their products, and dysfunction of the Eustachian tube. Gastro-esophageal reflux (GER) could also be a cause of this disease. Reflux of gastric contents from the nasopharynx to the middle ear is possible. **Objective:** To study the possible relationship between gastro-esophageal reflux and chronic middle ear effusion by evaluating the presence of pepsin in middle ear fluid of patients with chronic otitis media with effusion (OME). **Results:** All effusions collected from 40 children with OME contained pepsin protein in a concentration range of (523.25 – 1214.0 ng/ml) effusion. The average pepsin level in all effusion samples was 841.98 ng/ml(SD 179.82).The difference between the levels of pepsin and degrees of hearing loss was statistically significant [probability of overlap (P) value = 0.0001 (P value < 0.05)], and there is a significant positive correlation. [correlation-confident (r) = 0.691]. **Conclusion:** The presence of pepsin in MEE supports the relationship between gastro-esophageal reflux disease (GERD) and OME. Measurement of pepsin can be considered a reliable marker for assessment of reflux in children with OME. However, further research is needed to establish a definite association between GERD and OME by measuring pepsin/pepsinogen concentration in serum, gastric juice and MEE.

KEYWORDS: Otitis media with effusion, secretory otitis media, Gastro-esophageal reflux disease, Myringotomy, Ventilation tube.

INTRODUCTION

Otitis media with effusion is considered to be the most common cause of childhood deafness. Chronic secretory otitis media is a common disease in children, especially in developing countries. In these countries secretory otitis media may pass unnoticed for a long time and then develop slowly into a chronic condition. It may then cause hearing impairment **(Balle et al., 2000)**. Moreover, otitis media with effusion can lead to persistent pathological changes like atrophy, tympanosclerosis, and adhesive otitis media. This disease can present in different forms because of the large variation in the nature of the middle ear effusions, which can vary from a clear effusion without distinct signs of infection to a cloudy or purulent fluid **(Wielinga et al., 2001)**.

In spite of the common occurrence of secretory otitis media, its etiology and pathobiology are still largely unknown. Causes of this disorder are believed to be multifactorial, including viruses, allergy, bacteria and their products, and dysfunction of the Eustachian tube **(Salonen et al., 1989)**. Gastro-esophageal reflux (GER) could also be a cause of this disease. Reflux of gastric contents from the nasopharynx to the middle ear is possible because of the angle and immaturity of the Eustachian tube in children and infants, and the supine position in which infants are often placed **(Tasker et al., 2002).**

Mild forms of secretory otitis media may clear in few months' time by themselves or after the removal of the middle ear fluid. In persistent cases, surgical measures like adenoidectomy and placement of ventilation tubes become mandatory in the effort to achieve a cure. Even then, about 30% of the patients show continuing or recurrent disease after one year **(Salonen et al., 1989).**

GER is a common world-wide condition. In most people it remains physiologic. When the frequency or duration of GER is severe enough to induce symptoms or histologic changes of chronic inflammation, GER become pathologic and is termed GER disease (GERD) **(Bothwell et al., 1999).** GERD has been reported to result in a variety of medical problems, including malnutrition, iron-deficiency anemia, and respiratory difficulties **(Nelson et al., 1997).**

GER is a digestive disorder with many extradigestive complications. Every pediatrician is aware of its "routine" aspects (eg. post-prandial vomiting in a healthy baby, which disappears within the first year of life) and its dramatic complication (eg. failure to thrive) **(Contencin and Narcy, 1992).** Otolaryngologic manifestations of GER in children are increasingly recognized and defined in the literature. The exposure of the upper aero-digestive tract to gastric secretions results in numerous pathologic conditions. Chronic rhino-sinusitis, recurrent otitis media, chronic cough, and airway abnormalities, such as subglottic stenosis, recurrent croup, laryngomalacia, and reflex apnea, may be caused or exacerbated by GER **(Suskind et al., 2001).** Recently, some studies encountered patients with chronic therapy-resistant ear problem that only resolved after their coexisting GER was diagnosed to be the cause and consequently was treated successfully as such. This observation suggested that some cases of middle ear disease might be considered as another extra-esophageal manifestation of GER **(Poelmans et al., 2002).**

The middle ear cleft under normal conditions is void of bacteria, whereas the nasopharynx hosts micro-organisms in abundance, both pathogens and non-pathogens. The middle ear cleft is connected to nasopharynx through the Eustachian tube. The tubo-tympanum has several modalities by which it hinder bacterial invasion of the middle ear cleft, the mucociliary clearance system certainly being one of the most effective. Most middle ear infections develop when pathogens ascend from nasopharynx into the sterile middle ear cleft **(Ruhani et al., 1996).**

Gastric juice that refluxes into the middle ear will cause transient damage to the Eustachian tube and the middle ear mucosa before it can be neutralized, resulting in inflammation and ideal conditions for secondary bacterial colonization, leading to symptoms associated with glue ear. Therefore, it is thought that antireflux treatment could prevent otitis media with effusion **(Tasker et al., 2002).**

Children with pathologic GER and GER-induced otolaryngologic disease generally have an excellent response to medical therapy. A few require surgical intervention in the form of antireflux surgery **(Suskind et al., 2001).**

Aim of the work

To study the possible relationship between gastro-esophageal reflux and chronic middle ear effusion by evaluating the presence of pepsin in middle ear fluid of patients with chronic otitis media with effusion (OME).

PATIENTS AND METHODS

40 patients ranged from (3-8) years with Bilateral chronic OME, clinically and audiologically diagnosed among patients selected from ENT outpatient clinic of Al-Azhar University hospital) in the period from October 2017 to December 2019. patients were refractory to the usual conservative lines of treatment for more than 3 months and planned to be managed surgically for their OME. Exclusion criteria included patients with unilateral chronic OME, history of allergic disease or cleft palate (cause ET dysfunction) and Current use of an H 2 blocker or a proton pump inhibitor.

All patients were posted for bilateral myringotomy with ventilation tube insertion under General Anaesthesia.

Myringotomy was done by myringotomy knife, ventilation tube placed by crocodile forceps under microscope or by endoscope, At the time of myringotomy (before placement of the tube), effusion fluid was aspirated through myringotomy incision.

Postoperatively all patients were treated with antibiotics, decongestants and antihistamines. They were discharged after 24 hours and follow up regularly every 3 months.

The effusion fluid samples were centrifuged to separate cellular components, and the supernatant was stored at −80°C for later pepsin assay.

Total pepsin concentrations in effusion were measured with Enzyme-linked Immunosorbent Assay (ELISA) using human pepsin specific antibody, and the results were statistically analyzed. The kit is a competitive inhibition enzyme immunoassay for the in-vitro quantitative measurement of human pepsin in serum, plasma, tissue extraction samples, and other biological fluids.

All samples were brought to room temperature slowly and diluted according to the prediction of the pepsin concentration in ear effusion before assaying. If the pepsin concentration values for these samples were not within the range of the standard curve, further dilution was

performed to obtain the proper result. Fresh samples without long-time storage are recommended for the test to prevent protein degradation and denaturalization, which would finally lead to erroneous results. Samples were then loaded into ELISA kit wells and instructions were followed as per the kits' protocol.

This assay has high sensitivity and excellent specificity for the detection of human pepsin. The minimum detectable dose of human pepsin is typically less than 0.47 ng/ml.

RESULTS

Our study included children with a range of 3-8 years .The age divided into 2 age groups, (3-5) years (67.5%) and (5-8) years (32.5%). The mean age of the patients was 4.6 ± 1.46 years. The incidence of OME was highest in the (3-5) year's age group. (Table 1).

Table 1: Age distribution of cases.

AGE	Number of cases	%	Mean pepsin level	Standard deviation(SD)
(3-5) years	27	67.5%	828.1 ng/ml	164.7
(5-8) years	13	32.5%	870.8 ng/ml	212.2
T value		0.64		
P value		0.5305		

The difference between both age groups was insignificant in the incidence of OME (p value > 0.05)

There were 23 males (57.5%) and 17 females (42.5%). There is a slight male predominance in this study. (Table 2)

Table 2: Sex distribution of cases.

Sex	Number	%	Mean pepsin level	Standard deviation(SD)
Male	23	57.5%	879 ng/ml	171.9
Female	17	42.5%	791.9 ng/ml	183.2
T value		1.53		
P value		0.1365		

The incidence of OME between males and females was significantly not different (p value > 0.05).

Presenting Symptoms

Patients presented with 3 groups of symptoms;

- Symptoms of chronic middle ear effusion.

- Gastro-esophageal symptoms.
- Extra-esophageal symptoms.

Symptoms of chronic middle ear effusion: Patients presented with diminusion of hearing was seen in 100% of cases, the mother reported impaired speech and language in 52.5% of cases and 20% impaired school progress, and 37.5% had earache. (Table 3).

Table 3: Symptoms of chronic middle ear effusion.

Symptoms of chronic middle ear effusion	Number	%
Diminusion of hearing	40	100%
Earache	15	37.5%
Impaired school progress	8	20%
Impaired speech & language	21	52.5%

Gastro-esophageal symptoms: Patients presented with abdominal pain in 45% of cases, 37.5% had difficulty swallowing, 30% had nausea, 20% had vomiting and 15% had heartburn. (Table 4).

Table 4: The gastro-esophageal symptoms.

Gastro-esophageal symptoms	Number	%
Abdominal pain	18	45%
Nausea	12	30%
Vomiting	8	20%
Difficulty swallowing	15	37.5%
Heartburn	6	15%

Extra-esophageal symptoms: Patients presented with sore throat in 70% of cases, 62.5% had loss of appetite, 57.5% dry cough, 35% had halitosis and 27.5% had hoarseness'. (Table 5)**.**

Table 5: The Extra-esophageal symptoms.

Extra-esophageal symptoms	Number	%
Sore throat	28	70%
Loss of appetite	25	62.5%
Dry cough	23	57.5%
Halitosis	14	35%
Hoarseness	11	27.5%

Otoscopic finding in Tympanic membrane: Most common finding on otoscopy was dull, lusterless, amber coloured TM seen in 95% of cases. Absent cone of light was found in 20%

of cases. Interrupted and disturbed cone of light was found in 55% of cases. Air bubbles were found in 8% of cases. (Table 6).

Table 6: Otoscopic finding in T.M.

Tympanic membrane appearance	Number	%
Dull, lusterless, amber coloured	38	95%
Absent cone of light	8	20%
Interrupted and disturbed cone of light	22	55%
Air bubbles	8	20%

Pepsin concentration groups: The total pepsin concentrations of effusions and serum samples were measured with an enzyme-linked immune-sorbent assay (ELISA) using human pepsin-specific antibody.

Pepsin was detected in all effusion samples. The concentrations of pepsin in effusion samples were divided into 4 groups (Group A 17.5%, Group B 52.5%, Group C 10% and Group D 20%). (Table 7).

Table 7: Pepsin concentration groups.

Pepsin concentration	Number	%
Group A (500-700)	7	17.5%
Group B (700-900)	21	52.5%
Group C (900-1000)	4	10%
Group D (1000-1200)	8	20%

Relation between degree of hearing loss and level of pepsin: Most of the patients had moderate hearing loss and the mean hearing loss on audiometry was 31.63 dB (SD 7.88). The average pepsin level in all effusion samples was 841.98 ng/ml (SD 179.82).

The difference between the levels of pepsin and degrees of hearing loss was statistically significant [probability of overlap (P) value = 0.0001(P value < 0.05)], and there is a significant positive correlation [correlation - coeffient (r) = 0.691] (increase hearing loss by increase level of pepsin). (Table 8)

Table 8: Relation between degree of hearing loss and level of pepsin

Degree of hearing loss	Number	Mean pepsin level	Standard deviation (SD)
25 dB	16	740.5	108.6
30 dB	12	787.9	111.9
35 dB	4	1033.1	207.8

45 dB	6	974.2	148.7
50 dB	2	1199.0	21.2
			(P) value 0.0001
			correlation-coeffient **(r)** 0.691

The difference between both levels was significant (p value < 0.05)

DISCUSSION

Although otitis media with effusion continues to be one of the most prevalent childhood diseases, much controversy remains regarding its pathogenesis. OME is primarily a chronic inflammatory condition and the causes of inflammation are multifactorial. Because conventional treatment modalities have failed to eliminate the complication of OME, further research must target the cause and prevention of OME **(Butler and Williams, 2003).**

Scientists and clinicians know that gastric contents alter the mucosal surface of the esophagus. Recent research findings have shown that multiple episodes of short-term acid exposure, like that experienced in human reflux disease, produced more severe esophagitis with mucosal ulceration than one continuous episode of acid exposure **(Cassidy et al., 1992).**

Refluxed gastric contents not only affect the esophagus but also reach the hypo- and nasopharynx. The exposure of the upper aero-digestive tract to gastric secretions results in numerous pathologic conditions. Chronic rhino-sinusitis, recurrent otitis media, chronic cough, and airway abnormalities such as subglottic stenosis, recurrent croup, laryngomalacia, and reflex apnea, may be caused or exacerbated by GER **(Halstead, 1999; and Suskind et al., 2001).**

An increasingly important issue in pediatric otolaryngology is the relationship between chronic otitis media and GER. A connection between both disorders is recognized, but the underlying mechanism remains unclear. Vagal reflexes from the lower part of the esophagus might contribute. Another possible mechanism is thought to be the micro-aspiration of gastric contents into the throat with resultant damage to the Eustachian tube. The size and the shape of the immature ET in children can be blamed for the reflux of acid and pepsin from the nasopharynx into the middle ear **(Bluestone, 1996)**.

Contencin and Narcy (1991) first noted the potential relationship between OME and GER when they published a study documenting the presence of gastric juice in the nasopharynx, by detecting drops in nasopharyngeal pH, in subset of children with chronic or recurrent

rhinitis, with or without typical GERD symptoms. Reflux of gastric acid and pepsin from the nasopharynx into the middle ear is possible due to the angle of the immature ET in children. **Contencin et al. (1995)** later postulated that gastric contents in the nasopharynx may lead to inflammatory changes in the ET leading to ETD and subsequent OME.

Krishnan et al. (2002) conducted a study to determine whether the presence of gastric pepsin in tracheal aspirates of infants and children might be used as a reliable marker of the micro-aspiration of refluxed gastric contents. They successfully detected pepsin in 7 of 27 children with reflux symptoms alone and in 7 of 8 of those with chronic respiratory symptoms. In addition, pepsin was present in 31 of 37 children with a history of both reflux and chronic respiratory symptoms. Tracheal pepsin was not detected in any of the 26 children without GER or respiratory symptoms. Tracheal pepsin was found significantly more frequently in children with reflux symptoms than those without, particularly in children with both reflux and respiratory symptoms. They suggested that tracheal pepsin assay is a reliable marker of GER aspiration.

Brooks (1976) in his study showed 50% of the patients were in the age group of 5-7 years. Similar results were seen in the study conducted by **Reddy (1998).** In this work, the mean age was 4.6 years.

Tos and Stangerup (1985) have shown that male children have more incidence of OME than female due to male preponderance of childhood infection. In this work, there was slight male predominance in both age groups. Also, mean pepsin level higher in males (879 ng/ml) than in females (791.9 ng/ml), and this is in line with the fact that males are more susceptible to infection.

Paradise et al. (1997) reported no apparent gender based difference in the incidence of OME. In this work, the difference between both age groups was insignificant in the incidence of OME (p value > 0.05).

In this study

All effusions collected from 40 children with OME contained pepsin protein in a concentration range of (523.25 – 1214.0 ng/ml) effusion. The average pepsin level in all effusion samples was 841.98 ng/ml.

Diminusion of hearing was the most common symptom related to ear, abdominal pain was the most common gastro-esophageal symptom and sore throat was the most common extra-esophageal symptom.

On otoscopy, dull lusterless amber coloured TM was the common finding seen in 95% of cases, absent cone of light was seen in 20% of cases, interrupted and disturbed cone of light was found in 55% of cases and air bubbles was found in 8% of cases.

Most of children in our study had moderate hearing loss and average hearing loss was 31.63 Db. **Klausen et al.(2000)** have shown that OME can produce mild to moderate conductive hearing impairment, which can fluctuates, remains stable, or alternates with period of normal hearing. Of affected children, 55% have a hearing loss of more than 21dB in the speech frequency range. Another study found that 20% of children with OME had poorer pure-tone average than 35dB hearing level.

The difference between the levels of pepsin and degrees of hearing loss was statistically significant [probability of overlap (P) value = 0.0001 (P value < 0.05)], and there is a significant positive correlation [correlation-coeffient (r) = 0.691] (increase hearing loss by increase level of pepsin).

The presence of pepsin in middle ear effusion (MEE) supports the relationship between gastro-esophageal reflux disease (GERD) and otitis media with effusion (OME). Measurement of pepsin can be considered as a simple and reliable method for assessment of reflux in children.

Although no antireflux measures were used in this study, it's thought that the current data support the anti-reflux treatment in children with refractory middle ear inflammations like those with OME and in children suffering from recurrent attacks of otitis media.

CONCLUSION

The gastro-esophageal reflux (GER) is one of the contributing factors in the etio-pathogenesis of middle ear effusion (MEE) as gastric pepsin reaches the middle ear through the nasopharynx and the Eustachian tube to cause OME, and therefore, control of GER may play a role in the prophylaxis and management of OME and avoidance of tympanostomy.

The antibody used for pepsin assay is commercially available and stable to storage, and the assay itself can be performed on multiple stored specimens and requires little more than a microfuge and a micro plate auto-reader as equipment. So, the used technique of enzyme-linked immune-sorbent assay (ELISA) for detection of pepsin in the effusion of children with OME; using mono-specific anti-pepsin antibodies; can be considered a reliable marker for assessment of reflux in similar children specially those patients suspected of having other LPR- related otolaryngologic disorders. The presence of pepsin in MEE supports the relationship between gastro-esophageal reflux disease (GERD) and OME.

However, further research is needed to establish a definite association between GERD and OME by measuring pepsin/pepsinogen concentration in serum, gastric juice and MEE.

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