International Journal of Pediatric Otorhinolaryngology 78 (2014) 2250–2254

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Pepsin deteriorates prognosis of children with otitis media with effusion who undergo myringotomy or tympanostomy tube insertion

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ARTICLE INFO

Article history:
Received 20 June 2014
Received in revised form 14 October 2014
Accepted 16 October 2014
Available online 24 October 2014

Keywords:
Otitis media with effusion
Pepsin
Pepsinogen
Myringotomy
Tympanostomy tube insertion

ABSTRACT

Objective: To investigate the concentrations of pepsin and pepsinogen within the middle ear cavity and determine whether pepsin and pepsinogen affect the prognosis of children with otitis media with effusion (OME).

Methods: All middle-ear lavage fluid from patients with OME undergoing myringotomy (M subgroup) or tympanostomy tube insertion (T subgroup) was collected and pepsin and pepsinogen were detected using enzyme-linked immunosorbent assay. After close follow-up over 2 years, the effects of pepsin and pepsinogen on the prognosis of the patients with OME in the *M* and T subgroups were analyzed.

Results: The average pepsin and pepsinogen concentrations were significantly lower in the M subgroup ($n = 54$; 24.38 ± 16.10 mg/mL and 286.49 ± 91.95 mg/mL, respectively) than in the T subgroup ($n = 55$; 45.56 ± 16.60 mg/mL and 664.92 ± 107.06 mg/mL; $t = 2.484$, $P = 0.018$ and $t = 2.670$, $P = 0.011$, respectively). In the M subgroup, the average time to tympanic membrane healing and tympanic pressure restoration to normal was much longer in pepsin(+) patients (17.0 ± 2.0 days and 26.0 ± 2.5 days, respectively) than in pepsin(−) patients (14.0 ± 1.1 days and 22.0 ± 1.0 days; $t = 3.871$, $P = 0.001$ and $t = 5.734$, $P = 0.000$, respectively), and the hearing level of pepsin(+) patients with OME ascended to 13.08 ± 1.19 dB, which was much lower than that of pepsin(−) patients (18.29 ± 1.27 dB; $t = 11.001$, $P = 0.000$). In the T subgroup, the complication rate including otorrhea and myringosclerosis was much higher in patients with high pepsin concentrations than in those with low pepsin concentrations ($P < 0.05$). Finally, in both subgroups, the recurrence rates of OME in pepsin(+) or patients with high pepsin concentrations (34.6% [9/26] and 28.6% [10/35]) were significantly higher than those in pepsin(−) or low pepsin concentrations (10.7% [3/28] and 5.0% [1/20]; $\chi^2 = 4.456$, $P = 0.035$ and $\chi^2 = 4.420$, $P = 0.036$). However, pepsinogen had no significant effect on OME prognosis or recurrence.

Conclusion: Pepsin but not pepsinogen could postpone tympanic membrane healing and pressure restoration in children with OME undergoing myringotomy and increase the incidence of recurrence and complications including otorrhea and myringosclerosis for those undergoing tympanostomy tube insertion. Therefore, pepsin could be considered a poor prognostic factor for OME, further emphasizing the important role of pepsin in OME pathogenesis.

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1. Introduction

Otitis media with effusion (OME) is a kind of inflammatory disease characterized by middle-ear effusion (MEE) and hearing loss in children [1]. The pathogenesis of OME is very complicated, and eustachian tube dysfunction caused by mechanical obstruction of adenoid hypertrophy is considered a common factor, but very little is known about the chemical damage factors and inflammatory events in this disease process [2].

Laryngopharyngeal reflux (LPR), characterized by regurgitation of gastric contents into the upper aerodigestive tract, is considered an underlying etiologic factor of the development of OME in children [3,4]. A combination of factors, including toxicity of conjugated bile acids, osmotic damage from the refluxate, and proteolytic damage from gastric enzymes in the mucosa of the middle ear cavity, are involved in the pathogenesis of OME [5]. The proteolytic activity of pepsin, a major gastric enzyme, has attracted

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http://dx.doi.org/10.1016/j.ijporl.2014.10.026
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many researchers' attention, but a cause–effect relationship between pepsin in the middle ear and OME remains unclear [6]. In our previous study, we identified the presence of pepsin and pepsinogen in the middle ear and adenoid tissues and found a positive correlation of pepsin and pepsinogen levels between them, indicating that pepsin and pepsinogen may play an important role in pathogenesis of OME [7].

Myringotomy and tympanostomy tube insertion are the major operative treatments for OME, but complications such as otorrhea and myringosclerosis are inevitable and can affect patient prognosis [8]. Since pepsin and pepsinogen may play important roles in the pathogenesis of OME, could they also affect their prognosis? This remains unclear and no results have been reported to date.

In this study, we aimed to compare the concentrations of pepsin and pepsinogen in middle-ear lavage fluid from children with OME undergoing myringotomy or tympanostomy tube insertion. Meanwhile, this study sought to explore the underlying effects of pepsin and pepsinogen on the prognosis of patients with OME who undergo myringotomy or tympanostomy tube insertion.

2. Materials and methods

2.1. Study subjects

Children diagnosed with OME and adenoid hypertrophy were consecutively enrolled in this prospective study from May 2011 to May 2012 at the Department of Otolaryngology – Head and Neck Surgery, The Second Hospital, Xi'an Jiaotong University. Children aged 2–8 years undergoing myringotomy/tympanostomy tube insertion and adenoidectomy were included in the study and subsequent follow-up. Exclusion criteria were as follows: age 2–8 years, clinical diagnosis of adenoid hypertrophy without hearing problems, and myringotomy or tympanostomy tube insertion not required, or having taken medication to reduce stomach acidity, such as pump inhibitors, in the past 3 months preceding the start of the study. Informed consent was obtained from the parents of each participating patient and the research protocols were approved by the Ethics Committee of the Second Hospital, Xi'an Jiaotong University (registration number 2012092).

2.2. Collection of middle-ear lavage fluid from the patients with OME undergoing myringotomy or tympanostomy tube insertion

First, all subjects underwent adenoidectomy and myringotomy. If a MEE was present, regardless of viscosity, we extracted all of it and then flushed the middle ear cavity with 0.5 mL of sterile brine and collected the lavage fluid into an EP tube. A tympanostomy tube was inserted into the middle ear cavity if the MEE was thick. If no effusion was present, to gain pepsin and pepsinogen adherent to the middle ear mucosa, 0.5 mL of sterile brine was lavaged into the middle ear cavity and then collected into an EP tube and stored at −80 °C.

2.3. Collection of plasma

A total of 3 mL of venous blood was collected during surgery from each patient and then centrifuged to acquire plasma as previously described [7].

2.4. Pepsin and pepsinogen detection by enzyme-linked immunosorbent assay (ELISA) in middle-ear lavage fluid and plasma

The specific detection method was described elsewhere [7].

2.5. Postoperative follow-up of patients with OME undergoing myringotomy (M subgroup)

All the children in the M subgroup were followed up postoperatively every 2 days to observe tympanic membrane healing status. Once the tympanic membrane was healed, we recorded the time since myringotomy. The patients were then followed up sequentially every 2 days and an acoustic immittance test was used to measure the tympanic pressure until it changed to type A or As and we recorded the recovery period since myringotomy. Meanwhile, auditory brainstem response detection was used to confirm hearing level recovery.

2.6. Postoperative observation for complications of patients with OME undergoing tympanostomy tube insertion (T subgroup)

All of the children in the T subgroup were followed up every week from tympanostomy tube insertion to tube extubation or detachment for up to 1 year. During this period, complications such as tube blockage and otorrhea, granulation formation, myringosclerosis and cholesteatoma formation (temporal bone computed tomography scanning was adopted if necessary) were closely observed and recorded.

2.7. Judgment of postoperative recurrence for children in the M and T subgroups

All children in the M and T subgroup were followed up monthly for 2 years until the tympanic membrane had healed or the tube was extubated or detached. Recurrence was identified if the MEE appeared once again and was verified by an acoustic immittance test or endoscopy. The time from the first operation to the recurrence was recorded.

2.8. Statistical analysis

The SPSS 17.0 statistical software package (International Business Machines Corporation, Armonk, NY, USA) was used for the data processing. Continuous variables were expressed as mean ± SD, and Student's *t*-test was used to compare the means of two normally distributed independent and continuous variables. The Kaplan–Merier test in survival analysis was adopted to compare the positive rates of different groups after close follow-up. Differences were considered statistically significant at values of $P < 0.05$.

3. Results

3.1. 3.1. Clinical features of OME patients in children

A total of 109 patients with OME were enrolled into our study and undergoing either myringotomy (M subgroup, 29 boys and 25 girls, mean age, 4.7 ± 1.2 years) or tympanostomy tube insertion (T subgroup, 28 boys and 27 girls, mean age, 4.8 ± 1.0 years), and middle ear lavage fluid samples ($n = 109$) were collected during surgery. Meanwhile, complete follow-up data were collected after close follow-up lasting for 2 years. There were no significant differences in age or sex distribution between groups ($P > 0.05$).

3.2. Concentrations of pepsin and pepsinogen in middle-ear lavage fluid

The positive rates of pepsin and pepsinogen in the patients with OME were 69.7% (76/109) and 73.4% (80/109), respectively. Specifically, the positive rates of pepsin and pepsinogen in the M subgroup (51.9% [26/54] and 57.4% [28/54]) were markedly lower than those in the T subgroup (90.9% [50/55] and 94.5% [52/55])

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