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Main Article

Adenoid mast cells and their role in the pathogenesis of otitis media with effusion

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Abstract

Introduction: Otitis media with effusion (OME) is an inflammation of the middle ear in which a collection of liquid is present in the middle-ear space while the tympanic membrane is intact. The association between adenoid inflammation and OME has long been noted but the exact mechanism is still much debated. We studied the role of adenoid mast cells in the causation of OME.

Objective: To study the distribution and role of adenoid mast cells in the causation of OME

Methodology: A cross-sectional, prospective study was carried out in the otorhinolaryngologic clinic, department of otorhinolaryngology (ORL), Science University of Malaysia, from June 1999 to September 2001. A total number of 50 cases were studied. Twenty-five of these patients underwent adenoidectomy, while another 25 patients underwent adenoidectomy and myringotomy with ventilation tube insertion. The adenoid specimens from all patients were examined for the number of adenoid mast cells present, using light microscopy and toluidine blue as the staining agent. The results were analysed using SPSS version 10.0 computer software.

Result: The population of adenoid mast cells in children with OME was significantly greater than that in children without OME ($p = 0.000$).

Conclusion: The increased number of adenoid mast cells in patients with OME suggests that inflammation may play a role in this condition.

Key words: Adenoid; Otitis Media with Effusion; Mast Cell, Pathogenesis

Introduction

Most clinicians consider otitis media with effusion (OME) to result from eustachian tube dysfunction related to the adenoid, due to the proximity of the adenoid to the pharyngeal opening of the eustachian tube and to the improvement in OME seen following adenoidectomy. However, the exact role of the adenoid in the pathogenesis of OME has not been fully elucidated.

It has been suggested that the adenoid plays an important role in OME by mechanical and functional obstruction of the eustachian tube and by functioning as a source of bacterial antigens due to inadequate handling of bacteria during upper respiratory tract infection.[1]

Similarly, several authors have hypothesized that the adenoid may compress or obstruct the eustachian tube lumen, causing low middle-ear pressures and subsequent effusion formation.[2–4]

On the other hand, several studies have shown that the value of adenoidectomy in OME is not related to the adenoid size.[5,6] Other authors have observed no correlation between adenoid size and OME.[6,7]

Furthermore, Sade and Luntz did not find that adenoids played an obstructive role in the pathogenesis of OME.[8] Their histological study of the eustachian tube lumen in OME and acute otitis media failed to show any lumen obstruction or significant difference in lumen size in OME, acute otitis media and non-pathological specimens.

Collins *et al.*[9] suggested another possible mechanism – the 'adenoid mediator release' theory. They showed that children with fluid present in both ears had increased amounts of histamine in their adenoid tissue compared with children with no signs or symptoms of OME. They postulated that release of this powerful mediator of inflammation from the adenoid tissue is responsible for initiating and maintaining a local inflammatory reaction in the eustachian tube, which may eventually lead to development of a middle-ear effusion.

It has been shown by Dennis *et al.*[10] that histamine induces vasodilatation, increased vascular

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permeability and oedema of the eustachian tube and middle-ear mucosa. These inflammatory changes may represent indirect evidence that histamine contributes to eustachian tube dysfunction and OME.

Palva *et al.*[11] and Berger and Ophir[12] found increased mast cell numbers and histamine levels within the adenoids of patients with OME. Nakata and Suzuki[13] demonstrated a high level of histamine in the middle-ear effusions of chinchillas, induced by the introduction of immune complexes. Kiroglu *et al.*[14] performed electron microscopic examination of the adenoids of 28 children who had undergone adenoidectomy for OME, using as a control adenoids removed from 10 children during surgical removal of airway foreign bodies. These authors noted abundant mast cells in the adenoids of patients with OME, compared with controls.

The present study was performed to research the role of adenoid mast cells in the pathogenesis of OME, by examining the adenoid mast cell population of patients with OME and comparing it to that in patients without OME.

Materials and methods

We undertook a cross-sectional, observational–comparative study of patients who were diagnosed with enlarged adenoids, with or without OME, at the otorhinolaryngology clinic, Universiti Sains Malaysia Hospital, from June 1999 to September 2001.

Consent was obtained from the parents for the respective operation(s), in the usual manner.

Only patients in the three to 12 year age range were selected for the study. Their demographic data were recorded on a data collection form.

Selection criteria

Our inclusion criteria were: patients between the age of three and 12 years; patients suffering chronic adenoiditis without OME for at least six weeks, to serve as the control group; and patients suffering chronic adenoiditis with either unilateral or bilateral OME, to serve as the intervention group.

Our exclusion criteria were: symptoms and/or clinical signs of otitis externa; tympanic membrane perforation on examination, with or without infection; and the absence of symptoms and signs of OME for more than 12 months.

Symptoms

In the case of chronic adenoiditis, we specifically enquired about long term nasal blockage, nasal discharge, mouth-breathing, snoring and findings confirming obstructive sleep apnoea.

In patients with OME, we specifically enquired about ear blockage, otalgia, tinnitus and hearing impairment.[9,12]

Examination

All patients were examined by an otorhinolaryngologist or a senior otorhinolaryngology medical officer. Examination findings were noted, as follows.

The appearance of the patient was specifically examined for adenoid facies (i.e. opened mouth, broad upper lip, short nose, prominent upper teeth or triangular face). We performed anterior rhinoscopy in all cases and posterior rhinoscopy where possible, to confirm the presence of enlarged adenoids and to exclude other obstructive causes (e.g. deviated nasal septum or nasal polyp).

Examination of both ears was performed using either an otoscope or an operating microscope. The character of the tympanic membrane was determined, that is: normal, dull or retracted; colour (yellow, grey, blue or amber); and presence of fluid in the middle ear (i.e. air bubbles or a fluid level).

Rinne's and Weber's tuning fork tests were performed using 512 Hz tuning forks whenever possible or reliable and the findings recorded.[9,15,16]

Imaging

All patients then underwent a soft tissue, lateral neck X-ray (true lateral view).

We documented the size of the adenoids according to the radiological system described by Cohen *et al.*,[17] that is: 1+ = normal sized adenoids for a child of that age, along with a normal nasopharyngeal airway; 2+ = moderately enlarged adenoids, with moderate narrowing of the airway; 3+ = marked enlargement of the adenoids, with the airway nearly occluded; and 4+ = massive enlargement of the adenoids, along with total airway occlusion.

Hearing assessment

Hearing assessment was performed by certified audiologists, using tympanometry in three to 12 year olds, play audiometry in three to six year olds and pure tone audiometry in seven to 12 year olds.

Surgery

Surgery was performed under general anaesthesia. The adenoids were excised using curved curettes and a large mirror and headlight to inspect the nasopharynx. Curettage was performed with three strokes, that is, one median stroke and two lateral strokes, to ensure complete removal of the adenoids. The curettes used were appropriate for the size of the adenoids palpated.

Specimen collection and fixation

Adenoid tissue was kept in a 10 per cent formalin (fixation) container and sent immediately to the histopathology laboratory of the department of pathology, within the School of Medical Sciences. Tissue was processed in the routine manner and embedded in paraffin. A representative section of the entire adenoid tissue was obtained and a 5 μm slice created using a microtome knife.

Staining

All slices were: rinsed with distilled water for two minutes; stained with toluidine blue for 10 minutes; rinsed back with distilled water for two minutes;

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dehydrated with 95 per cent alcohol and absolute alcohol for two minutes each; cleared in xylene; and finally made ready for mounting. The toluidine blue stained the mast cell cytoplasmic granules metachromatically purple.

Mast cell identification and counting

All specimens on the slide were examined using a Nikon SE light microscope (Nikon, Yokohama, Japan). Cell identification was performed with the help of a pathologist. The distribution of mast cells was examined in the various regions of the adenoid tissue under $\times 400$ magnification. The total number of mast cells in 10 high power fields was counted manually and recorded for each specimen. Results were expressed as mean number of cells per high power field.

Data analysis

Results were stored on a computer-based filing system and were analysed using the commercially available statistical programme for social science (SPSS) version 10.0 software. The significance level was set at $p = 0.05$ for all statistical analysis; a p value less than 0.05 was considered as significant. The help of a medical bio-statistician was obtained to analyse the data.

Results

Mast cell count

The number of mast cells per high power field ranged from 0.1 to 3.9 in the adenoids of children with normal middle ears; the mean count was 1.160 cells per field.

By contrast, the adenoid specimens of children with OME harboured more mast cells per high power field, numbering from 1.1 to 8.0; the mean count was 3.228 cells per field.

Data histograms for both groups were skewed, as shown in Figures 1 and Figure 2.

Due both to this result and to the small sample size (less than 30 in each group), a non-parametric test for two independent samples was used (Mann–Whitney test) to analyse the number of mast cells.

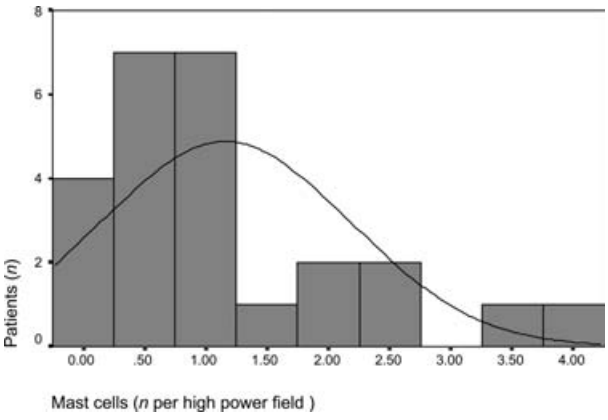

FIG. 1

Number of adenoid tissue mast cells in patients with chronic adenoiditis (control group).

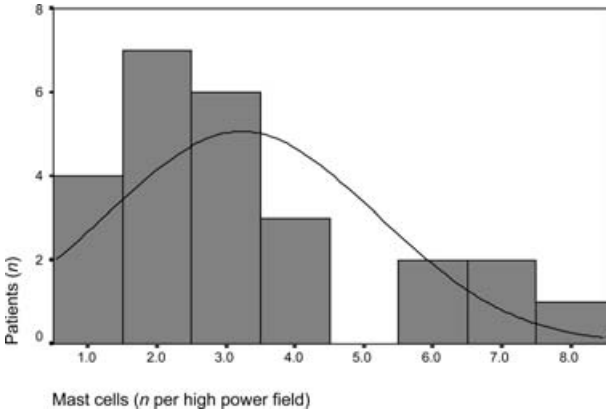

FIG. 2

Number of adenoid tissue mast cells in patients with otitis media with effusion (tested group).

Statistical analysis of the data confirmed that the adenoid mast cell population of children with OME was significantly greater than that of children without OME ($p = 0.000$).

Discussion

The relationship between adenoid inflammation and OME was first recognized in 1842 by Macleod Yearsly, who performed the first adenoidectomy for conductive hearing loss, and was later described in detail by Wilhelm Meyer in 1868.[18]

Certain racial groups are believed to have a higher incidence of OME: American natives (American Indians and Eskimos), the Maori of New Zealand, natives of Guam, Greenland Eskimos, Australian aborigines and Laplanders.[19] Differences in OME rates in these races may reflect differences in access to medical care, socioeconomic status, and anatomical or biological susceptibility.

The demography of this study was peculiar to the homogenous society of Kelantan, Malaysia (a state in north-east Malaysia). Our patients who underwent adenoidectomy and myringotomy with grommet insertion were all of Malay extraction, except for two Chinese children (who underwent adenoidectomy).

The frequent coexistence of enlarged adenoids and OME has all too often been taken as proof of a direct causal link between these two associated phenomena. Some studies[3,20,21] have concluded that OME is caused by encroaching, enlarged adenoids,

TABLE I

ADENOID MAST CELLS IN BOTH GROUPS

Patients	*n*	Mast cells per hpf	
		Range	Mean
Children with OME	25	1.1–8.0	3.228 ± 1.967
Children without OME	25	0.1–3.9	1.160 ± 1.020

OME = otitis media with effusion; hpf = high power field

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TABLE II

COMPARISON WITH ADENOID MAST CELL COUNTS IN PREVIOUS STUDIES

	Present study		Berger & Ophir[12]	
	Patients (*n*)	Mast cells per hpf (mean)	Patients (*n*)	Mast cells per hpf (mean)
Children with OME	25	3.2280 ± 1.967	40	3.1778 ± 1.902
Children without OME	25	1.1600 ± 1.020	36	1.5956 ± 0.960
Significance*	$p = 0.0000$		$p = 0.0001$	

*Comparing results for children with and without otitis media with effusion (OME). hpf = high power field

as follows; the middle-ear effusion is created by transudation when a vacuum in the middle-ear cleft results from enlarged adenoids obstructing the opening of the eustachian tube. However, histopathological studies contradict this theory.

Sade and Luntz[8] studied eustachian tube lumen pathology in specimens from persons with OME and found that the eustachian tube lumens were patent but their cross-sectional areas tended to be smaller than those of non-inflammed eustachian tubes. Sando and Takahashi[22] also found that the midcartilaginous portion of the eustachian tube tends to be moderately inflamed in persons with OME but that no eustachian tube obstruction was present.

Collins *et al.*[9] were the frst to suggest the possible role of adenoid mast cells in the pathogenesis of OME. They postulated the 'adenoid mediator release' hypothesis, i.e. that OME is a result of eustachian tube inflammation due to the release of inflammatory mediators from the adenoids, which may initiate and maintain a local inflammatory reaction in the eustachian tube and middle ear.

Subsequently, several investigators demonstrated high histamine contents in the adenoids of OME patients. A morphological study by Kiroglu *et al.*[14] studied the adenoids of OME patients using light and electron microscopy and demonstrated an abundance of histamine. Palva *et al.*[11] studied crushed adenoid tissue from 36 children with OME and found that the adenoid tissue histamine content was significantly raised, ranging from 1.4 to 11.7 μg/ml, with an average of 5.9 μg/ml. The normal plasma concentration of histamine is less than 7 ng/ml, but histamine concentration in adenoid tissue from normal children had not been measured for ethical reasons.[11]

We carried out the present study based on the assumption that the adenoids of children with OME should harbour an increased number of mast cells and an indirectly raised amount of histamine. Our results are similar to those obtained by Berger and Ophir;[12] we have shown that the adenoids of children with OME contain a significantly increased number of mast cells.

The mast cells we observed tended to be round or oval but occasionally were much more elongated. Their size varied considerably. Mast cells are a virtual pharmacopoeia of biologically active compounds, and their activation will result in the release of histamine and a variety of other mediators (such as leukotrienes, prostaglandins, eosinophilic chemotactic factor of anaphylaxis and platelet-activating factor) that participate in the inflammatory reaction.

The degranulation of adenoid mast cells, releasing their mediators of inflammation, may cause severe pathophysiologic derangements of the eustachian tube, leading to the development of middle-ear effusion. Histamine is a potent chemical mediator of inflammation, affecting the permeability of vessels, and may participate in the production and maintenance of an effusion in the tympanic cavity. Inflammatory mediators might be important causative factors in the pathogenesis and prolongation of OME.

An immediate type of hypersensitivity (allergic reaction) would be a possible trigger for adenoid mast cell degranulation. This is supported by the experimental study of Lowman *et al.*,[23] who found that adenoid mast cells release histamine in response to anti-immunoglobulin E antibodies.

Conclusions

In our study, the adenoids of children with OME were observed to contain an increased amount of mast cells, compared with the adenoids of children without OME. The benefits of adenoidectomy in children with OME thus include removal of a potential source of inflammatory mediators in the vicinity of the eustachian tube (i.e. the adenoids); this procedure needs further evaluation.

- **The association between adenoid tissue and otitis media with effusion (OME) has long been noted, with the exact mechanism still being debated. This study investigated the role of adenoidal mast cells in the causation of OME**
- **The population of adenoid mast cells in patients with and without OME were compared**
- **The population of adenoid mast cells was significantly greater in patients with OME, raising the possibility of a causal link between adenoid mast cells and OME**

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