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Review Article

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The Middle Ear: A Major Target of Upper Respiratory Tract Allergic Disease

David S Hurst

Associate Clinical Instructor, Tufts University School of Medicine, retired David S Hurst, Associate Clinical Instructor, Tufts University School of Medicine, USA

***Corresponding author**
David S Hurst, Associate Clinical Instructor, Tufts University School of Medicine, USA

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The diagnosis and treatment of chronic otitis media with effusion (OME)has been a long-standing conundrum in medical practices. Why? Partly because past studies provide little support of a relation of allergy to otitis mediate due to the poor sensitivity of earlier methodology for determining atopy. In order to understand the inflammatory processes that allow OME to persist it is essential to characterize the cellular constituents and their degree of activity in the diseased middle ear.

The middle ear is essentially a fifth sinus which happens to harbor the organ of hearing. It is an extension of the upper respiratory tract and aerated via a narrow orifice, similar to the paranasal sinuses. It is our contention that the middle ear behaves like the rest of the respiratory tract and that what has been learned about the atopic response in mucosa of the sinuses and lungs may be applied to the ear to help in understanding OME. Yet while hay fever, asthma, dermatitis, etc respond to the traditional anti-allergic medicines and antihistamines, OME itself shows little benefit from these treatments.

Persistence and/or recurrence of fluid in the middle ear leaves the surgeon to rely on repeated myringotomy and placement of tympanostomy tubes(M&T) in order to remove the fluid and provide aeration so as to restore hearing and avoid longterm consequences of hearing loss and mastoid disease. The medical literature dating back to 1931, as reported by Proetz, Shambaugh, Zhang, Draper, Doyle, Pelikan, Ojala, McMahan, Tomonaga, Nsouli, Lasisi, Nguyen, Tian, Sobol, Smirnova, Shim, Smirnova, Luong, and Hurst supports the allergic causes of otitis media with effusion (OME) and that "ETD responds best to immunotherapy" [1]. (Table I)

Unfortunately, surgical approaches such repeated M&T, as well as eustachian tube dilatation, do not address the underlying etiology. Identification of factors involved in the chronicity of otitis media is an essential step in the treatment and ultimate prevention of chronic disease. The relation of otitis media with effusion (OME) to allergy remains controversial. Clinical studies have shown that patients with OME have allergies that can be diagnosed by standardized intradermal (IDT)or skin prick testing (SPT) and in vitro testing [2-4]. When these allergies are properly treated, the patient's effusion will resolve [3-6].

The association of OME with allergy does not prove causality. Technology in the past 40 years has made astonishing advances in understanding what is occurring in the middle ear to cause OME. Immunologic studies have confirmed OME to be an immune mediated disease [7]. However, despite reports of the presence in middle ear fluid of various mediators of an allergic response, including histamine, leukotrienes, prostaglandins, and various cytokines, few otologists credit allergy with a direct role in the pathophysiology of middle ear disease, possibly due to the lack of instruction regarding allergic mechanisms during surgical training [7].

In order to characterize the relation of allergy or infection to OME we measured ECP, MPO, and tryptase in effusion from 97 patients. Thirty-six pre-school children (age 14 months to 6 years), 41 children of school age (6-18 years), and 20 adults were selected in a consecutive, prospective manner [8]. All had documented hearing loss, flat tympanograms and effusion of a minimum of 3 months duration unresponsive to antibiotic and/or decongestant therapy. Ear effusions were collected at the time patients underwent routine M&T.

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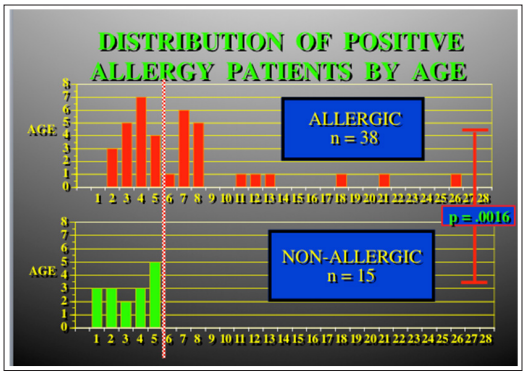
Age: Infants and young children 14 months to 6 years of age presented as a mixture of both PUR-OME and OME. Fewer than 20% of patients older than 6 years present with infection (PUR-OME). All patients over 6 years old had allergies. Both Gates, et al. and Yellon, et al. observed that older children typically tend to have more chronic OME, have different levels of cytokines in their effusion, and need repeated myringotomy and tympanostomy [9,10]."

Table I: Studies of OME Patients with Allergy Confirmed by Skin Testing [1].

Year	Author	# Patients	% Atopic	Resolution
'42	Dohlman67	178	56 %	
'42	Mao68		29 %	of pathologically
				deaf children
			2 %	of normal children
'49	Jordan	123	74 %	98 %
'58	Solow	50	72 %	
'61	Lecks	82	88 %	
'65	Fernandez	113	55 %	95 %
'65	Whitcomb	38	100 %	87 %
'67	Draper	340	53 %	
'81	Hall	92	100 %	
'81	McMahan	119	93 %	86 %
'86	Sanz	20	30 %	
'88	Tomonaga	259	72 %	of OME
'90	Hurst	20	100 %	0% non-atopic
'91	Becker	35	34 %	SPT
'94	Nsouli	104	78 %	86 %
'94	Corey8	89	61 %	
'96	Hurst	73	87 %	
'98	Psifidis	148	59 %	78 %
'04	Doner	22	38 %	SPT
'08	Lasisi	80	80 %	SPT
'08	Hurst	89	100 %	89% resolve
	21 Studies	2326 total	Ave 68%	0% of Controls
		Patients	7 > 87%	



Infants and young children 14 months to 6 years of age presented as a mixture of both PUR-OME and OME [9].

Finding both mast cells and its mediator tryptase in middle ear fluid confirmed that a Th2 driven immune response was present in a majority of ears that have chronic effusion. These findings support the hypothesis that middle ear mucosa is capable of an allergic response and that the inflammation within the middle ear of most OME patients is allergic in nature [8].

The appearance of mast cells in airway epithelium is an indication of disease and not a normal feature [11]. Initial reports of mast cells in humans had been limited to cadaver temporal bones, in which the number of mast cells were significantly increased in chronic inflammatory reactions [12,13]. In the initial stages of serous otitis mast cells are found in the lamina propria and the pars flaccida [14,15]. Histopathologic examination of effusion demonstrates that both eosinophils and neutrophils are integral components in these secretions [10]. Mast cells were thought to "play an important role in the pathogenesis of chronic otitis media through the release of their active biochemical mediators [10]. The atopic status of that author's patients was not determined.

Effusion Subjects: We measured tryptase and ECP in middle ear effusions from 38 individuals (i.e. 44 ears, including 6 pairs) who presented with refractory OME to a solo community-based otolaryngologist [16]. (Table II) Subjects included 18 children (age 32 months to 6 years) and 15 children of school age (6-18 years) selected in a random, prospective manner. Five adults (age 55 to 69) with eustachian tube dysfunction served as controls. None were immunodeficient nor exhibited congenital malformations. All had documented hearing loss, flat tympanograms and effusion of a minimum of 2 months duration unresponsive to antibiotic and/or decongestant therapy. Among the 33 diseased patients were several children with no known antecedent infections who presented after failing a school hearing test. Serum and MEE were collected at the time patients underwent routine myringotomy and placement of tympanostomy tubes (M&T).

Table II [16]: Characteristics of 39 Patients with Otitis Media with Effusion

	TOT	CONTROL	PUR-OME	OME	(PUR and OME)
# Patients	38	5	7	26	33
# Ears	44	5	8	31	39
Age IN YEARS (mean)		67,9	5,5	7,5	7,29
Tryptase (mg/L)		1,3	2,55	4,77	4,63
Mean + SEM		0,2	0,35	0,91	0,74
Tryptase					
> 2µg/L	23	0	5	18	23
< 2 µg/L	21	5	3	13	16
ECP (µg/L)		2,66	174,16	109,2	122,5
MEAN +/- SEM		1,05	62,54	21,95	21,6
ECP levels in (n) Patients					
>10 µg/L	34	0	8	26	34

< 10 µg/L	10	5	0	5	5
Ears with a positive Elisa					
+AE	32	0	6	26	32
+AE/NR	8	2	1	5	6
-AE	4	3	1	0	1

+AE = atopy with effusion noted; -AE = no atopy with effusion noted; AE/NR = atopy not related

A second cohort of five children with 8 diseased ears (ages 5.2 to 16 years) were selected randomly for biopsy. All 5 patients had serum ELISA testing. Four other patients who had no signs of effusion or infection but were undergoing routine tympanoplasty for dry perforations served as controls. Biopsies from both normal and diseased patients were taken from the promontory of the middle ear following approval of the Franklin Memorial Hospital (Farmington, Maine) Committee on Ethics and Human Experimentation and with patient or parental consent. Working through the myringotomy incision, a 2 mm diameter sample of mucosa was elevated with a microcurette and removed using a microcup forceps. (Figure 1) [16].

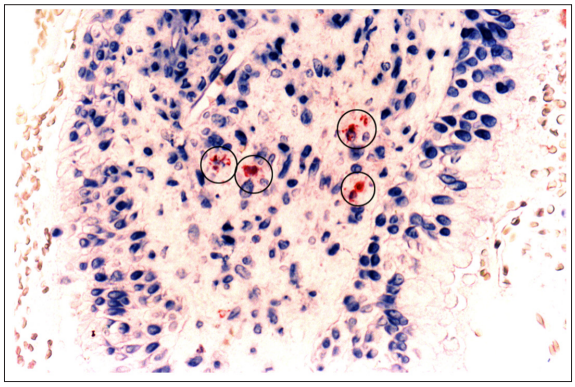


Figure 1: Anti-tryptase antibody (AA1) staining of mast cells (circled) [16].

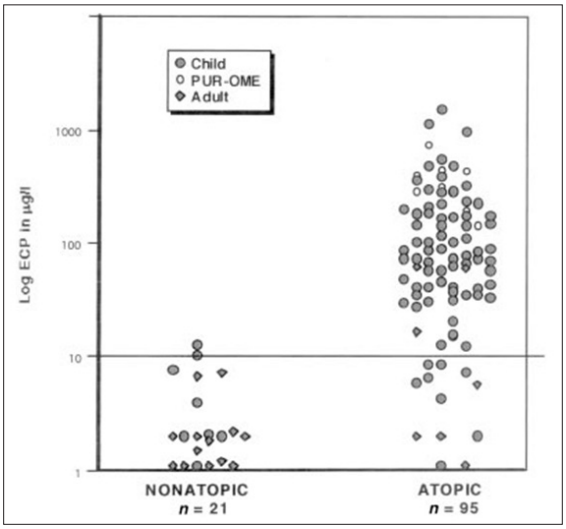
Diagnostic studies involving serum skin testing for allergy have shown little consistent results, partly due to the significant difference between intradermal (IDT) and skin prick testing (SPT) wherein the general allergists prefer SPT vs otolaryngologists who prefer intradermal testing as being twice as sensitive [17]. (TABLE III).

Ears that typify episodes of recurrent acute otitis media which quickly resolve between infections were excluded from the study. Patients designated as having OME were those who maintained effusion beyond 2 months. The biopsy samples were fixed in acetone which had been precooled to -20°C. The fixative included the proteinase inhibitors phenyl methyl sulfonyl fluoride (2 mM) and iodo acetamide (20 mM). Tryptase in the effusion was measured by a double antibody radioimmunoassay (Tryptase, Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) using a monoclonal antibody marked with radioactive I.

The dilution of the effusion specimens in this study is an important consideration. Assuming an average volume of 0.3 mL of effusion diluted during collection with 2 mL of saline in order to wash the thick mucoid samples from the 20 French suction tube, the absolute tryptase concentration in those middle ears in which tryptase was measurable (mean 6.46µg/l) was actually 6 to 7 times greater than that recorded in Table II and represents a mean of 38.8-45.2µg/l. Mast cells as well as their chief mediator, tryptase, were present in the mucosal biopsies of 6 of 9 ears from 8 patients with chronic effusion, all of whom were atopic to an average of 10 allergens. Mast cells were present in the mucosa20 and submucosa in allergics but absent in controls. The diseased ears demonstrated granulocytes in the mucosa which stained positive for ECP, indicating the presence of eosinophils [14].

To further characterize the relation of allergy or infection to OME we measured ECP, MPO, and tryptase in effusion from an additional 97 patients [8]. (Table IV) Thirty-six children (age 14 months to 6 years), 41 children of school age (6-18 years), and 20 adults were selected in a consecutive, prospective manner. All had documented hearing loss, flat tympanograms and effusion of a minimum of 3 months duration unresponsive to antibiotic and/or decongestant therapy. Ear effusions were collected at the time patients underwent routine M&T. Atopic Status: Eighty-one percent of this second group of 97 OME patients (79/97) were atopic [18]. Among the children, 93% (72/77) were atopic. (Table III) [18].

Table III [18]: ECP and atopic status in 116 patients with ear effusions



Mediator levels in effusions: The inflammatory response by eosinophils, neutrophils and mast cells in the middle ear was distinctly different depending on the patient's atopic status ($p<0.001$). ECP was elevated (>10 µg/l) in 86.1% (68/79) of ears of atopic patients (mean 165.8µg/L). Tryptase was elevated (mean 4.8 µg/L) in the effusion from 64% (23/36) of atopic patients. Tryptase was below 2µg/L in all 7 non-atopic patients as well as in 1 PUR-OME and 12 atopic patients. There was no correlation of tryptase to either MPO or ECP (Spearman $p>0.05$). The highest levels of MPO were found in ears which had a superimposed infection at the time of myringotomy (PUR-OME). Neutrophils were significantly active in all atopic ears, producing mean MPO levels 53 times higher than that measured in non-atopic. The inflammatory response by eosinophils, neutrophils, and mast cells in the middle ear8 was distinctly different depending on the patient's atopic status ($P<0.001$) [18].

Table IV [17]: Comparison of Results of 1:20 Skin Prick (SPT) vs Intradermal (IDT) testing of Patient P.E.> with chronic middle ear disease as done by both a General Allergist and an ENT Allergist

	General Allergist	General Allergist	ENT Allergist
PATIENT HF	+ by Prick	+ by intradermal	+ by intradermal
Dust P			X
CAT	X	X	X
DOG			X
Dust F			X
Grass			X
Ragweed		X	X
Trees	X	X	X
Weeds	X		X
Goldenrod			X
Cockroach			X
Molds:			X
Alternaria			
Hormodendrum			X
Other Molds			X
TOTAL POSITIVE	5	3	17
TOTAL TESTED	27	22	17

Table V: Mean mediator levels in 116 middle-ear effusions from 97 patients with OME [18].

	Non-atopic	Atopic	Total
Effusion			
No. of Ears	21	95	116
Mean ECP	3.38	165.82	
SD	3.50	240.26	
+ SEM	0.76	24.65	
P<0.0001			
Effusion MPO			
No. of Ears	18	51	69
Mean MPO	115.96	6231	
SD	12532	8018	
+ SEM	29.54	1122	
P<0.0001			
Effusion Tryptase			
No. of Ears	8	49	57
Mean Tryptase	134	4.78	
SD	039	5.09	
+ SEM	0.14	0.73	
P=0.009			

Conclusion

Our observations add to the body of evidence demonstrating that the cells and cytokines essential to the production of a Th2 immune mediated hypersensitivity reaction (atopy) are present in the majority of ears that have chronic effusion. This study provides confirmation on a cellular level that mast cell mediators measured in effusion of atopic patients arise from actively degranulating mast cells identified in the local tissue lining the middle ear cleft. Neither tryptase nor ECP levels were elevated if the patient was not a topic [8].

Immunohistochemical staining of biopsy material from normal ears showed no evidence of either mast cells or eosinophils but did demonstrate both cells to be present within the mucosa of 80% of ears from atopic children with OME.

The inflammatory response by eosinophils, neutrophils and mast cells in the middle ear is distinctly different between atopic and non-atopic patients($p<0.001$) [16]. These findings provide further evidence that eosinophils and mast cells, both essential to a Th-2 driven immune response, are active in the majority of ears from atopics with chronic OME and support the hypothesis that: middle ear mucosa, similar to that of the rest of the upper respiratory tract, is capable of an allergic response [19-21].

Thus, it is apparent that any child or adult considered for a second set of PE Tubes should also be evaluated for allergies as the underlying cause of their chronic middle ear disease, as immunotherapy offers the best opportunity for and the most long-lasting resolution of OME.

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