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CLINICAL & BASIC RESEARCH

Nasal Allergy and Otitis Media
A real correlation?

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التهاب الأذن الوسطى والأرجية الأنفية

علاقة حقيقية؟

دزيدوريوا بسالي، جيوليو سيسار بيسالي، ماريا ليوريالوا، أنتونيوا رومانو، ليوسا بيلوسي، فرانسيسكو ماريا بسالي

ABSTRACT: ***Objectives:*** The correlation between middle ear pathology and nasal allergy has been debated for almost 30 years. This study aimed to evaluate the relationship between otitis media with effusion (OME) and persistent allergic rhinitis symptoms *versus* intermittent rhinitis in children. ***Methods:*** The study included 100 atopic children (52 boys, 48 girls) aged 5–9 years with otological symptoms who were patients of the University of Siena Hospital, Italy. Ear, nose and throat evaluations, tympanometry, skin prick tests (SPTs), mucociliary transport time (MCTt) and Eustachian tube function tests were performed. ***Results:*** The SPTs revealed 50 children sensitised to *Dermatophagoides pteronyssinus*, 34 to grass pollen and 16 to *Parietaria*. Of all patients, mild symptoms were intermittent in 19 children and persistent in 18; moderate/severe symptoms were intermittent in 22 and persistent in 41. Tubal dysfunction was present in 25 children, whereas middle ear effusion was present in 45 children undergoing myringotomy. The MCTt was slower in the persistent group (21 ± 2 mins) *versus* the intermittent group (16 ± 2 mins) with a significant difference (P <0.01). Mean eosinophil cationic protein (ECP) values in the middle ear effusions of children who had undergone myringotomy were 251 ± 175.2 µg/L, and mean ECP blood values were 25.5 ± 16.3 µg/L, with significant differences (P < 0.001). ***Conclusion:*** There was a significant association between OME, delayed MCTt, ECP values in middle ear effusion and persistent symptoms of allergic rhinitis. These results suggest a direct involvement of the middle ear mucosa as a target organ in persistent forms.

Keywords: Otitis Media; Nasal Allergy; Children; Genetic Predisposition; Eustachian Tubes; Italy.

الملخص: الهدف: العلاقة بين أمراض الأذن الوسطى وأرجية الأنف كانت موضع نقاش لفترة تقارب 30 سنة. تهدف هذة الدراسة إلى تقييم العلاقة بين التهاب الأذن الوسطى مع الانصباب والتهاب الأذن الأرجي المستديم إزاءالتهاب الأذن المتقطع عند الأطفال. الطريقة: شملت الدراسة 100 طفلا منتبذ (52 صبيا، 48 بنتا) أعمارهم 9-5 سنوات عندهم أعراض بالأذن، وهم من مرضى مستشفى جامعة سردينيا، إيطاليا. تم عمل فحوصات شملت تقييم الأذن والأنف والحلق، قياس الطبلة، وخز الجلد، وقت نقل المخاط الهدبي، وفحص عمل النفير. النتائج: فحص الوخز بين وجود 50 طفلا حساسا إلى Dermatophagoides pteronyssinus، إلى 34 إلى طلع العشب، و 16 إلى Parietaria. من كل المرضى، الأعراض المتقطعة الخفيفة كانت عند 19 طفلا، المستديمة الخفيفة عند 18، والمتوسطة إلى الشديدة المتقطعة عند 22 والمستديمة عند 41. خلل الأداء الأنبوبي كان موجود عند 25 طفلا بينما أنصباب الأذن الوسطى كان موجود عند 45 طفلا ممن خضعوا لعملية بضع الطبلة. وقت نقل المخاط الهدبي كان أبطأ عند المجموعة المستديمة (2 ± 21 mins) إزاء المجموعة المتقطعة (2 ± 16 mins) مع فارق معتد به (P <0.01). متوسط قيم البروتين الكاتيوني لليوزينية عند انصباب الأذن الوسطى للأطفال الذين خضعوا لبضع الطبلة كانت 175.2 ± 251 µg/L. ومتوسط قيم دم ECP كانت 16.3 ± 25.5 µg/L مع فارق معتد به (P <0.001). الخلاصة: كان هناك ترابط معتد به بين التهاب الأذن الوسطى مع الانصباب، تأخر أوقات نقل المخاط الهدبي، قيم ECP لانصباب الأذن الوسطى و الأعراض المستدامة لالتهاب الأنف الأرجي. هذة النتائج تشير إلى علاقة مباشرة للغشاء المخاطي في الأذن الوسطى كعضو الصدمة عند الأعراض المستدامة.

مفتاح الكلمات: التهاب الأذن الوسطى؛ أرجية الأنف؛ الأطفال؛ أهبة وراثية؛ النفير؛ إيطاليا.

Advances in Knowledge

- *This research demonstrated the close relationship between persistent rhinitis and otitis media with effusion (OME).*
- *The mucosa of the nasal cavities and the pharyngeal portion of the tube have the same histological structure and thus, the same physiological target. The defense of the middle ear comes not only from the valve mechanism of the Eustachian tube (ET), but also from the effectiveness of mucociliary clearance. The minimal persistent inflammation affecting the rhinopharynx and the ET in persistent allergic rhinitis prevents the middle ear from returning to a stable physiological state. In these cases, the middle ear mucosa, subjected to continuous allergenic stimulation, can develop a specific hyperactivity with local production of specific immunoglobulin E and mediators of the allergic reaction such as eosinophil cationic protein.*

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Application to Patient Care

- *The ear nose and throat specialist, as well as the general practitioner, need to be made well aware of the data from this study.*
- *In the presence of a middle ear effusion, particularly if it is resistant to common medical and surgical approaches, the state of the nose should be carefully evaluated to detect a possible allergic predisposition or pathology. If such a chronic disease is present, it should be treated to avoid repeated acute episodes and the sequelae of chronic middle ear effusion.*

Nose and middle ear are correlated entities, which belong to a system called the rhinopharyngotubal unit or the "unified airspace".[1] The key element to middle ear disease, in both physiological and pathological conditions, is the Eustachian tube (ET), whose functions are middle ear ventilation, clearance, and mechanical and immunological defence.[2] The ET opens during swallowing (once per min during waking hours and once every five mins during sleep), chewing and yawning to balance the mucosal reabsorption of air (0.5–1 mm^3 per min).

The drainage of secretions from the middle ear is carried out by the mucociliary transport (MCT) system, which is localised in the cartilaginous portion of the ET. The functioning of the MCT system of the ET is enhanced by the surface tension lowering substance (STLS), which allows the rolling of the mucus. The periodical opening of the ET fibro-cartilaginous portion prevents the aspiration of inflammatory or infectious secretions from the rhinopharynx. Furthermore, the ET is provided with specific defence mechanisms by antimicrobial substances such as lysozymes and by resident microbial flora which compete with pathogens. The local lymphoid tissue is scattered in the superficial layer of the chorion of the cartilaginous portion and is particularly plentiful around the pharyngeal *ostium*.[3]

Studies on the pathogenesis of otitis media (OM) have identified interactions between infection, allergic reactions and ET dysfunction.[4,5] In particular, Martines *et al*., who studied the audiological characteristics of otitis media with effusion (OME) in two cohorts of children (atopic and non-atopic), found that atopic children are more prone to developing bilateral OME, to present with a type B tympanogram (flat, clearly abnormal) and to have a lower hearing threshold compared to non-atopic children.[6,7] The link between OM and nasal allergy was also confirmed through the study of the joint effect of atopy and upper respiratory tract infection (URTI) in the development and/or maintenance of middle ear effusion. In fact, the relative risk for OM, in presence of URTI, increases 271 times among the allergic population.[8]

In a previous study, we showed that specific immunogobulin E (IgE) are significantly increased, when compared with blood values, in middle ear effusion in patients allergic to *Dermatophagoides pteronyssinus* (*Der. pt.*).[9] To elucidate whether allergy plays a role in the pathogenesis of OM, the aims of the present study were to evaluate the relationship between OME—defined as the presence of middle ear fluid without signs and/or symptoms of infection (otalgia, fever)—and persistent allergic rhinitis symptoms *versus* intermittent rhinitis in children

Methods

The present study, conducted between September 2008 and May 2010, was approved by the hospital and research committees of the University of Siena, Italy. It received no financial support from any source. After obtaining informed consent from the parent/caregiver of each child, we enrolled 100 atopic children (52 boys and 48 girls), aged between five and nine years, who had otological symptoms (aural fullness, hearing loss) and persistent or intermittent nasal allergic symptoms according to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification.[10]

The classification of allergic rhinitis into seasonal, perennial and occupational types has the merit of being simple and didactic; however, it does not always correspond to the clinical picture of allergic rhinitis. For example, in pollinosis the respiratory symptomatology is conditioned by latitude, climatic conditions and atmospheric pollution; these factors can all influence the environmental pollen load and hyperactivity of the exposed subjects.[11] In the last decade, a classification has been added to the ARIA guidelines that makes reference to the intensity and the duration of the symptoms. This allows a

stepwise therapeutic approach for the treatment of "persistent minimal inflammation" involving the respiratory mucosa which is often present in the absence of symptoms. This classification was used in the selection of the patients.

The term 'intermittent' was defined as symptoms present for less than four days a week or for less than four weeks; 'persistent' was defined as symptoms present more than four days a week and longer than four weeks. The severity of the symptoms was classified as 'mild' (absence of sleep disturbance, no impairment of daily activities, of school or work, no troublesome symptoms) or 'moderate-severe' (when one or more of the previous factors were present).[10]

For each child, a clinical evaluation of the ear, nose and throat (ENT), a skin prick test (SPT), a mucociliary transport time (MCTt) test, a tympanometry and an ET function test were performed. Eosinophil cationic protein (ECP) values were measured only in the middle ear effusions of the 45 children with bilateral type B tympanogram, undergoing myringotomy after six month's follow-up. Patients with both ear and nasal symptoms were selected because the intention was not to demonstrate the relationship between OME and nasal allergy which has already been demonstrated by several studies.[2,4,5,12] Rather, the present research aimed to increase the knowledge about the relationship between OME and chronic *versus* intermittent nasal allergenic symptoms. For the same reason, monosensitised subjects to three different allergens responsible for persistent or intermittent nasal symptoms independent of the season or climatic changes were selected. SPTs were performed on the volar side of the forearm. Allergen-containing vials for a standardised panel of respiratory allergens were used (Lofarma S.p.A., Milano, Italy). They were adapted for the SPTs by means of disposable plastic skin needles. Allergens were standardised and titrated in diagnostic biological units (DBU). The patients' nasal symptoms were treated on demand with oral antihistamines or leukotrienes according to the suggestion of their family paediatrician.

The ET function was evaluated as follows: (1) after a baseline tympanogram with a GSI TympStar impedenzometer (Grason-Stadler Inc., Eden Prairie, Minnesota, USA), the patient was asked to drink a glass of water in order to reduce middle ear pressure (Toynbee manoeuvre) and then another tympanometric recording was carried out; (2) the patient was instructed to close their mouth, occlude the nostrils with two fingers, and try to blow air through the nose in order to create positive pressure in the middle ear (Valsalva manoeuvre). A final tympanometric recording was then taken. The ET was considered 'completely occluded' when no changes in the tympanometric curve were registered after both the Toynbee and Valsalva manoeuvres, or 'partially occluded' when only the Valsalva manoeuvre had obtained positive effects. All the tests were performed randomly by two trained ENT specialists.

To determine the nasal MCTt, a mixture of charcoal powder and 3% saccharine was used. As charcoal powder is an insoluble tracer, it efficiently monitors the transport of the particles entrapped into the outer gel layer; saccharine, on the other hand, is a soluble marker and gives the time of clearance into the inner sol layer of ciliated epithelium.[12] The MCTt was evaluated as follows: a small quantity of charcoal powder and 3% saccharine mixture was applied into the nose on the head of the inferior turbinate by cotton swab. The time needed to detect the presence of the charcoal powder on the oropharynx wall, checked by using a tongue depressor every minute, was considered the MCTt. This method is simple to execute, non-invasive and inexpensive. It furnishes reliable results in adults and children on the efficiency of the clearance system and on the eutrophic condition of the respiratory mucosa.[13] It can also be usefully employed to follow-up any medical therapy, including local nasal immunotherapy, as we have previously reported.[14]

A total of 45 children, allergic to *Der. pt*. and who, on follow-up six months after enrolment, had a type B tympanogram, were selected for a myringotomy with insertion of a ventilation tube. Blood and middle ear effusion samples were collected to measure ECP, a marker of eosinophil activation, by fluorescent-enzyme immunoassay (FEIA) (CAP System ECP-FEIA Method, Pharmacia Biosystems GmbH, Freiburg, Germany).

The statistical analysis was performed using the Student's T-test. The MCTt times were reported in mins ± standard deviation (SD). ECP concentration values were reported in μgr/L ± SD.

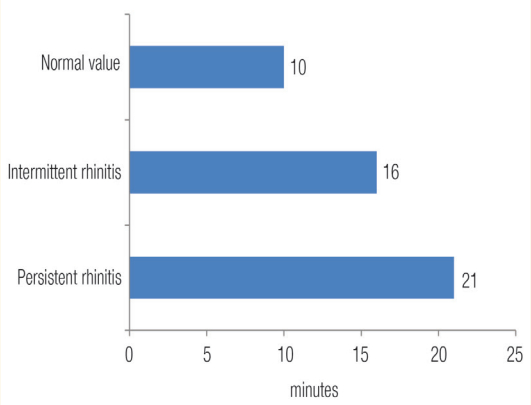

Figure 1: Mean values of mucociliary transport time (charcoal powder) in allergic children reporting persistent or intermittent symptoms and otologic complaints.

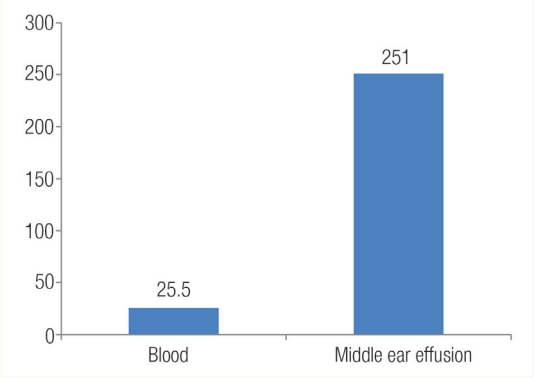

Figure 2: Eosinophil cationic protein mean levels (µgr/L) in blood and middle ear effusion in 45 children allergic to *Dermatophagoides pteronyssinus* and reporting a type B tympanogram at follow-up six months after enrolment.

Results

A total of 50 children (50% of the cohort) were found by SPTs to be sensitised to *Der. pt*. Among them, 41 (82%) reported persistent symptoms from moderate to severe and nine (18%) had intermittent moderate to severe nasal obstruction. Of the 34 children found to be sensitised to grass pollen, 20 (58.8%) had intermittent symptoms, whereas the other 14 (41.2%) had mild to moderate persistent nasal obstruction and watery rhinorrhoea. Finally, among 16 children allergic to *Parietaria*, only four subjects (25%) reported persistent mild symptoms. Mild intermittent symptoms were present in 10 subjects (62.5%), whereas two children (12.5%) reported intermittent symptoms from moderate to severe [Table 1].

The MCTt was significantly delayed in the persistent rhinitis group of all subjects (21 ± 2 mins) compared to the intermittent group (16 ± 2 mins) with a significant difference (P <0.01) [Figure 1]. Both groups of children with OME and either persistent or intermittent allergic rhinitis exceeded normal values for the charcoal powder MCTt (8 ± 3 mins in children and 13 ± 2 mins in adults).[13]

All children with OME were followed up every six months after their enrolment. Among the children allergic to *Der. pt.* (all on monthly follow-up visits), 45 had a bilateral type B tympanogram. At the end of the six-month follow-up period, they all underwent a myringotomy with ventilation tube insertion. Five (10%) of the children allergic to *Der. pt.* had a type C tympanogram. Among the 34 children allergic to grass pollen, nine cases (26.5%) had a type A tympanogram (normal), and 25 children (73.5%) had type C (indicating a significantly negative

Table 1: Allergic sensitisation, symptoms severity-duration and tympanograms

	Pts	Intermittent rhinitis* n (%)		Persistent rhinitis** n (%)	
		Mild	Moderate/Severe	Mild	Moderate/Severe
Der. pt.	50		5 (10.0) 4 (8.0) C B		41 (82.0) B
Grass	34	9 (26.5) A	11 (32.3) C	14 (41.2) C	
Parietaria	16	10 (62.5) A	2 (12.5) C	4 (25.0) C	

Der. pt. = Dermatophagoides pteronissinus; pts = patients; A = tympanogram classification type A/normal; B = tympanogram classification type B/flat, clearly abnormal; C = tympanogram classification type C/indicates significantly negative pressure.

** The presence of the symptoms for less than four days a week or for less than four weeks.*

*** The presence of the symptoms for more than four days a week and longer than four weeks.*

Mild symptoms = absence of sleep disturbance, no impairment of daily activities, including school or work, no troublesome symptoms; Moderate/Severe symptoms = one or more of the previous symptoms are present.

pressure). Among the *Parietaria*-positive children, the tympanograms were classified as type A in 10 cases (62.5%) and type C in six (37.5%) [Table 1].

Tubal dysfunction was present in 25% of all patients; in particular the ET tubes were completely occluded in 16 *Der. pt.*-positive children, in five grass pollen-positive patients and in four *Parietaria*-positive ones.

The mean ECP values in the middle ear effusions of children undergoing myringotomy were 251 ± 175.2 µg/L and were significantly elevated as compared to the mean ECP blood values at 25.5 ± 16.3 µg/L (P <0.001) [Figure 2].

Discussion

As far as allergy is concerned, raised levels of eosinophils, basophils and histamine have been found in the nasal mucosa of young children with chronic otitis, and chronic or recurrent OME. This seems to be associated with allergic rhinitis in 24% to 89% of cases.[6–8] Several studies have underlined a correlation between allergic inflammation and alteration of the mucociliary clearance. The mediators released by the nasal mucosa during allergic inflammation influence MCT, modify the cilia function and structure[15] and the production and rheological characteristics of the secretion.[16] The results of the current study have demonstrated a statistically significant difference between the MCTt of subjects reporting perennial allergic symptoms compared to those who complained only about intermittent mild symptoms.

In a recent study, Kirtsreesakul *et al*.[17] described alterations to the mucociliary clearance in subjects affected by allergic and non-allergic rhinitis; these changes are more evident in allergic patients and they are proportional to the cutaneous reactivity during skin tests to the alteration of parameters of respiratory functionality (peak expiratory flow index), and to symptom severity (total nasal symptoms score), but not to the number of sensitising allergens. The results of the present study concur and affirm that the MCT is impaired in patients with OME and allergic rhinitis. This is an expression of the underlying mucosal inflammation and should lead physicians to adopt a stepwise therapeutic approach.

Data from the literature show that allergy is a risk factor for OME[18] and that atopic children are more prone to OME recurrence after medical therapy[19] and/or adenoidectomy *versus* non-atopic children (P <0.005) and that immunotherapy significantly improves middle ear disease.[20] In the current study, children with persistent OME and nasal allergy were found to have tympanograms positive for ET dysfunction more frequently than children complaining of intermittent symptoms. This study has established a significant association between OME and persistent allergic rhinitis whereas the correlation between OME and intermittent allergic forms was less significant. It may be that the continuous allergic inflammation affecting the rhinopharynx and the ET in patients with persistent allergic rhinitis prevents the middle ear from returning to a physiologically stable state.

The oedema and vessel congestion of the respiratory mucosa in allergic inflammation hinder the ventilation function of the ET; rhinorrhoea and abundant secretions alter the function of drainage and of the ET aeration of the middle ear.

On the ground of these considerations, it can be hypothesised that the middle ear mucosa, subjected to continuous allergenic stimulation, can sensitise itself to develop a specific local hyperactivity with the accumulation of eosinophils, T helper type 2 (Th2) lymphocytes, and positive cells for interleukin 4 (IL-4) and IL-5, with local production of specific IgE and mediators of the allergic reaction.[21]

In the patients examined, mean blood ECP values far above normal values proved and confirmed that the patients were atopic. However, higher levels of ECP in middle ear effusions, when compared with those measured in the blood (with a statistically significant difference), together with our previous identification of high specific IgE values in middle ear effusion from patients allergic to *Der. pt*.,[9] strongly suggest the direct involvement of middle ear mucosa as a target organ in OM—in patients affected by persistent allergic rhinitis with local production of specific IgE and release of ECP in the middle ear effusion.

Only the 45 subjects who had a bilateral type B tympanogram over the six-month follow-up period (corresponding to the 90% of the examined sample) underwent transtympanic drainage and the measurement of ECP, as a marker for the allergic inflammation, in the blood and in the secretions from the middle ear. This could be considered a limitation of our study. Nevertheless,

the myringotomy and the transtympanic drainage with the possible measurement of the inflammatory mediators in the endotympanic effusion, have to be considered invasive procedures, especially because OME has a fluctuating course and a high rate of spontaneous resolution.[22]

Conclusion

The findings of this study suggest that children affected with persistent nasal allergy and auricular symptoms should be accurately assessed. In these cases, the objective evaluation of the rhinopharyngotubal area, performed by flexible endoscope, may reveal a pale and swollen mucosa. The nasal mucociliary function can be easily evaluated by an MCT test which, if delayed, would suggest allergy as an aetiology for the child's middle ear disease.

Tympanometry and tubal tests are useful to study the tubal opening, but they are not useful for providing data about clearance and tubal defensive functions. In children with OME, tympanometric dysfunction correlates more significantly with the delay of nasal MCTt than with tubal function tests. This study's findings of increased middle ear ECP and delayed MCTt in persistent allergic rhinitis supports the hypothesis that chronic OME is related to the patient's allergic disease.

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