
The role of nasal allergy in chronic secretory otitis media

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Background: Chronic secretory otitis media (SOM) has multifactorial causes, and nasal allergy is suspected as one of these causative factors.

Objectives: To investigate the possible role of nasal allergy in SOM in adults and to determine the diagnostic value of nasal challenges with allergens (nasal provocation tests) combined with tympanometry for the diagnosis of this disorder.

Methods: In 69 young adults with chronic or recurrent SOM, 173 nasal challenges with allergens were performed by anterior rhinomanometry combined with tympanometry (pure-tone air conduction tympanometry). In 42 control subjects with only allergic rhinitis and no history of middle ear disease, 42 nasal challenges with allergens were repeated and combined with tympanometry. The study design was a placebo-controlled comparison.

Results: Of the 69 patients, 54 developed 129 positive nasal responses of various types ($P < .01$), 117 of which were accompanied by significant changes in middle ear pressure ($P < .01$). No significant tympanometric changes ($P > .10$) were recorded during the 42 positive nasal responses in control subjects.

Conclusions: These results may confirm the occurrence of chronic SOM in some adult patients and the possible involvement of nasal allergy in chronic SOM. The nasal challenges with allergen performed by rhinomanometry, combined with tympanometry, seem to be a valuable supplementary tool for the diagnosis of this disorder.

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INTRODUCTION

Secretory otitis media (SOM) or otitis media with effusion, in its acute and chronic (recurrent) form, is a common disorder in children,^{1–5} but chronic SOM also occurs in adults.^{2,3,6,7} Acute SOM forms are usually caused by bacterial infections,^{1–3,5,8} whereas in the chronic SOM forms, multifactorial causes may be involved.^{1–4,6–9} The association of chronic SOM forms with eustachian tube (ET) dysfunction has already been unequivocally confirmed.^{1–15} Previously, the pathogenesis of inflammatory disorders of the middle ear (ME) has been investigated from various viewpoints.^{1–6} The chronic SOM form has an important effect on hearing.^{1–3,5,9–12} The role of the nasal mucosa in the pathogenesis of chronic SOM has clearly been recognized.^{1–9,13,14–27} Although the involvement of nasal allergy in ET dysfunction and in SOM has already been demonstrated,^{1–4,7–9,14,17–27} the diagnostic and therapeutic procedures for inflammatory disorders of the ME, and SOM in particular, vary.^{1–7,9–12,14} Some investigators performed nasal challenges with allergens^{4,21–23,25,27} or histamine²⁴ to analyze the role of nasal allergy in chronic SOM. However, the methods used in nasal provocation tests (NPTs), the subjects studied, the variables recorded, and the results gathered have varied.^{4,21–28} Few data are available to demonstrate the direct causal role of the nasal allergy, appearing primarily in the nasal mucosa, in ET dysfunction and

in the secondary response of the ME. This study investigates (1) the possible causal role of nasal allergy in chronic SOM in adults, (2) the clinical features of the middle ear responses (MERs) in relation to the nasal response (NR) to allergen challenge and its particular types, and (3) the diagnostic value of NPTs with allergen, combined with tympanometry.

METHODS

Patients

Sixty-nine patients, having been referred to the Department of Allergy and Immunology, Institute of Medical Sciences “De Klokenberg,” Breda, the Netherlands, volunteered to participate in the study. In these patients, young adults aged 16 to 26 years, with a history of bilateral chronic SOM since childhood, nasal allergy was suspected. They had recurrent symptoms of rhinitis, especially nasal obstruction, and chronic or recurrent otitis media, pressure or a “plugged-up” feeling in their ears, autophony, popping and cracking, tinnitus, otalgia, and hearing loss to some extent. In all these patients, various degrees of otoscopic changes were found.

The tympanic membrane expressed a bluish red color or erythema, opacification, sometimes an air-fluid level, or bubbles. In most patients, the mobility of tympanic membrane was diminished and a retraction of tympanic membrane, from a slight degree to an atelectasis, was found. Three patients showed a convex (bulging) of tympanic membrane. All patients were previously treated with various antibiotics, glucocorticosteroids, decongestants, H₁-receptor antagonists, and inflation of the ET. All patients had previously undergone an adenoidectomy, tonsillectomy, and repeated myringotomy. Some of them also had ventilation tubes inserted.

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None of these patients had received immunotherapy, oral corticosteroids, or nasal cromolyn. All patients underwent a routine diagnostic evaluation, consisting of disease history, physical examination, radiography of paranasal sinuses, basic laboratory examination, bacteriological examination of the nasal secretions and sputum, blood leukocyte and eosinophil count, nasal secretion cytogram, skin tests, serum paper radioimmunosorbent test (PRIST) and radioallergosorbent test (RAST), and screening tympanometry. In addition, nasal histamine thresholds were determined and 173 nasal challenges with various inhalant allergens (NPTs) were performed by rhinomanometry, combined with tympanometry. Patients were investigated during a period without manifest ear and nasal complaints and without symptoms of an acute infection. No short-acting H_1 -receptor antagonists or nasal decongestants were given for 48 hours before this study. The local ethics committee reviewed and approved this study. Oral informed consent was obtained from all participants in this study.

Control Group

Forty-two young adults with allergic rhinitis, confirmed by positive history, skin test results, and nasal challenges with allergens, but without any history of any ME disease and with normal otoscopic findings, volunteered to participate as control subjects in this study. Subjects underwent 42 nasal challenges with allergens using rhinomanometry, which were repeated and supplemented with tympanometry.

Allergens

Dialyzed and lyophilized allergen extracts (Allergopharma, Reinbek, Germany) were diluted in phosphate-buffered saline (PBS) and used in concentrations of 500 biologic units per milliliter (BU/mL) for skin tests and 5,000 BU/mL for NPTs. If indicated, the higher dilutions of the allergen extracts were used for the skin tests and the NPTs. A survey of the allergens used is given in Table 1.

Skin Tests

The intracutaneous tests were performed and evaluated after 20 minutes and after 6, 12, 24, 48, 72, and 96 hours, according to a standard routine schedule. A skin wheal reaction (>7.5 mm in diameter) appearing within 20 minutes after the intradermal injection was considered a positive immediate skin response. A reaction occurring 6 to 12 hours later was regarded as a positive late skin response, and a skin induration appearing more than 24 hours later (usually 36–72 hours) was considered to be a positive delayed skin response.^{26,27}

NPTs and PBS Control Tests

The NPTs with allergens were performed by the rhinomanometric technique, described previously.^{25–28} The nasopharynx-nostril pressure gradient (NPG) values (ΔP , expressed in centimeters of water), recorded by this technique, were considered the basic parameters of the nasal mucosa response

Table 1. Survey of the 173 Allergens Used

Allergen	Positive skin test result (n = 173)	Nasal response	
		Positive (n = 129)	Negative (n = 44)
<i>Dermatophagoides pteronyss</i>	49	38	11
<i>Dermatophagoides farinae</i>	7	4	3
Animal dander			
Dog	6	5	1
Cat	14	10	4
Hamster	4	2	2
Guinea pig	3	3	0
Feathers			
Pigeon	5	4	1
Canary	8	5	3
Parakeet	3	3	0
Pollen ^a			
Grass mix 1	22	16	6
Grass mix 2	15	12	3
Flower mix	10	7	3
Tree mix	18	14	4
Weed mix	9	6	3

^a Grass mix 1 includes *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*; grass mix 2, *Festuca pratensis*, *Holcus lanatus*, *Agrostis alba*, and *Anthoxanthum odoratum*; flower mix, *Dahlia variabilis*, *Solidago virgaurea*, *Primula variabilis*, and *Forsythia suspensa*; tree mix, *Betula pendula*, *Corylus avellana*, *Juniperus communis*, and *Salix alba*; and weed mix, *Artemisia vulgaris*, *Plantago lanceolata*, *Rumex acetosa*, and *Taraxacum officinale*.

(nasal obstruction). The NPTs were performed according to the following schedule¹: initial (baseline) values were recorded at 0, 5, and 10 minutes²; PBS control values were recorded at 0, 5, and 10 minutes after a 3-minute application of PBS to the nasal mucosa of the nonintubated nasal cavity by a saturated wad of cotton wool on a nasal probe, inserted under the medial turbinate³; test values were recorded similarly after a 3-minute application of allergen at 0, 5, 10, 20, 30, 45, 60, 90, and 120 minutes, then every hour up to the 12th hour, and then every second hour between the 24th and 38th hour and between the 48th and 56th hour. The NR was considered positive when the mean NPG values after the allergen challenge increased by at least 2.0 cm H_2O (mean $\pm$ SE, 1.2 ± 0.3 cm H_2O) with respect to the mean PBS values recorded during at least 3 consecutive intervals. The NPG changes occurring within 60 minutes after the allergen challenge were considered a positive immediate NR; those appearing within 4 to 12 hours, a positive late NR; and those occurring later than 24 hours, a positive delayed NR. Allergens for the NPTs were chosen with respect to the patient's positive history and positive skin test results (Table 1).

In each patient, a control nasal challenge with PBS was also performed according to the same schedule as used for the NPTs with allergen. A 2-day interval was always allowed between 2 consecutive tests.

Tympanometry

Tympanometry was performed before and during all nasal challenges with allergens and PBS control tests by a tympanometer (Micro Tym 2 Portable Tympanometer; Welch Allyn, Skaneateles Falls, New York). The variables recorded were (1) the middle ear pressure (MEP), expressed in millimeters of water (1 daPa = 1.02 mm H₂O); and (2) compliance (also called static admittance), expressed in cubic centimeters. The tympanometric variables (MEP values) were recorded at the equivalent intervals corresponding to the rhinomanometric NPG values. The normal MEP values for adults vary from -150 to 150 mm H₂O (daPa). The normal compliance peak should appear between 0.2 and 1.4 cm³ at a pressure of 0 mm H₂O.^{6,9-12,25}

Statistical Analysis

The NRs and the MERs to allergen challenge and the control tests with PBS in the individual patients were statistically evaluated by the Wilcoxon matched-pair signed rank test, comparing the NPG or MEP values recorded after the allergen or PBS challenge at each of the time points with the mean prechallenge baseline values. Each of the NRs and MERs recorded in the individual patients was compared with the PBS control response recorded in that patient and statistically evaluated by the generalized multivariate analysis of variance model (generalized MANOVA model).²⁷ The mean values of the NRs (NPG value changes) and the mean values of the MERs (MEP value changes) of the same type were compared with the mean values of the PBS control responses, at each of the recorded time points, and statistically evaluated by the Mann-Whitney *U* test. The statistical evaluation of the MEP changes was always performed separately for each of the ears (right and left) and then the mean from both the *P* values was calculated and presented in results. *P* < .05 was considered statistically significant for all tests used.

RESULTS

Nasal Responses

Of the 69 patients in whom 173 NPTs were performed, 54 developed 129 positive NRs, 35 isolated immediate NRs

(IINRs), 41 isolated late NRs (ILNRs), 26 dual late NRs (DLNRs) (immediate plus late), 19 isolated delayed NRs (IDYNRs), 8 dual delayed NRs (DDYNRs) (immediate plus delayed), and 16 negative NRs (NNRs) (Table 2 and Fig 1A, Fig 2A, and Fig 3A). The remaining 15 patients demonstrated 28 NNRs. The differences between the positive NRs and NNRs were statistically significant at all intervals (*P* < .001). The positive NRs were significant with respect to the prechallenge baseline values and the PBS control tests (*P* < .001 for both). The NNRs did not differ significantly either from the prechallenge baseline values or the PBS control tests (*P* > .10 for both). The particular types of NRs demonstrated significant positivity with respect to the appropriate PBS control responses. The significance of the particular NR types was as follows: IINR, *P* < .001; ILNR, *P* < .001; DLNR, *P* < .01 for immediate and late; IDYNR, *P* < .01; and DDYNR, *P* < .01 for immediate and *P* < .05 for delayed. The 16 NNRs recorded in 54 patients and the 28 negative responses recorded in 15 patients did not demonstrate any significant NPG changes compared with the PBS control tests (*P* > .20 and *P* > .10, respectively). No significant differences were found in the appearance and course of particular NR types with respect to the individual allergens (*P* > .10).

The 173 PBS control tests did not display any significant changes in the NPG values with respect to the NPG baseline values (*P* > .10).

Middle Ear Responses

Of the 129 positive NRs, 117 (31 IINRs, 39 ILNRs, 22 DLNRs, 18 IDYNRs, and 7 DDYNRs) were accompanied by significant changes in MEP values, which means that the slightly negative MEP increased significantly in negativity (*P* < .01) (Table 2 and Fig 1B, Fig 2B, and Fig 3B). The significance of the changes in the MEP values recorded during the particular types of MER, with respect to the MEP values measured during the PBS control tests, was as follows: 31 isolated immediate MERs (*P* < .01), 39 isolated late MERs (*P* < .001), 22 dual late MERs (*P* < .01 for immediate and late), 18 isolated delayed MERs (*P* < .05), and 7 dual delayed MERs (*P* < .02 for immediate and *P* < .05 for

Table 2. Survey of Particular Types of Nasal and Middle Ear Responses

Response to NPT (n = 173)	Significant changes in MEP ^a			No changes in MEP
	Total No.	Accompanied by otalgia ^b	Accompanied by a decrease in hearing	
Positive NRs (n = 129)	117	98	71	12
Isolated immediate (n = 35)	31	25	19	4
Isolated late (n = 41)	39	34	25	2
Dual late (n = 26)	22	18	12	4
Isolated delayed (n = 19)	18	15	11	1
Dual delayed (n = 8)	7	6	4	1
Negative NRs (n = 44)	9	9	6	35

Abbreviations: MEP, middle ear pressure; NPT, nasal provocation test (challenge); NR, nasal response.

^a Increase in negativity of the slightly negative MEP.

^b Subjective decrease in hearing confirmed by audiometry.

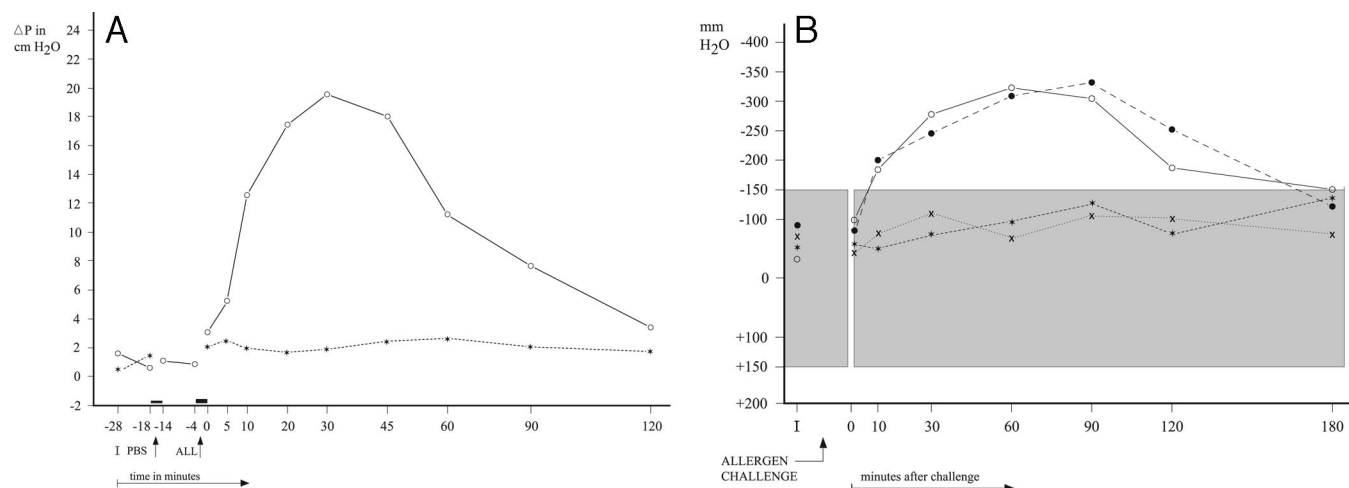


Figure 1. The isolated immediate nasal response (IINR) to allergen challenge (A) and the middle ear response accompanying the IINR (B). A, The mean nasopharynx-nostril pressure gradient values were recorded after the allergen challenge during 31 positive IINRs (open circles) and 31 phosphate-buffered saline (PBS) control tests (asterisks). B, The mean values of middle ear pressure were recorded during 31 positive IINRs (open circles indicate right ear; closed circles, left ear) and 31 PBS control tests (x marks indicate right ear; and asterisks, left ear). ALL indicates allergen challenge; I, initial value (baseline).

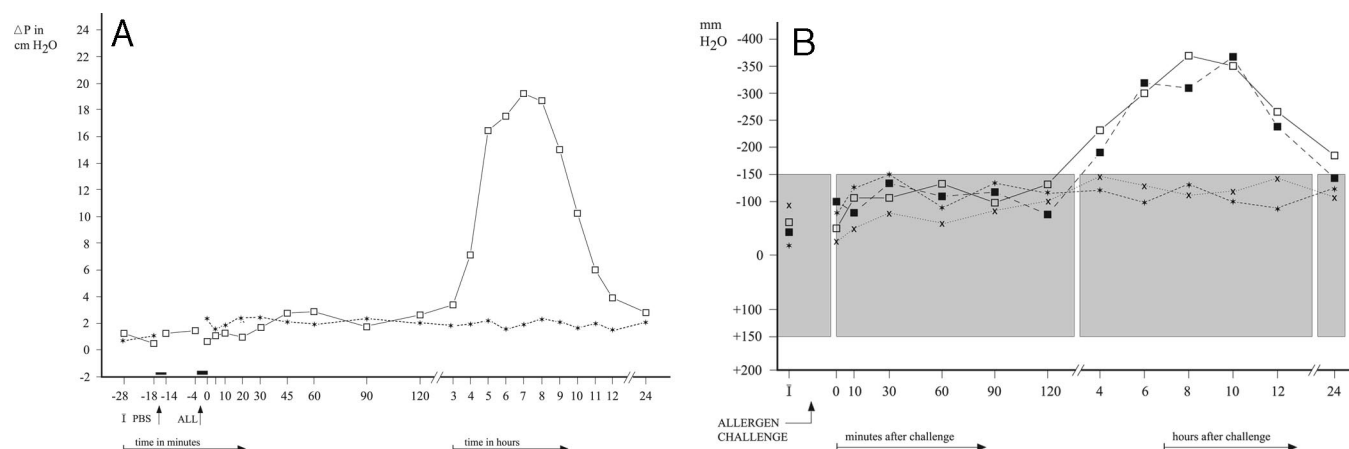


Figure 2. The isolated late nasal response (ILNR) to allergen challenge (A) and the middle ear response accompanying the ILNR (B). A, The mean nasopharynx-nostril pressure gradient values were recorded after the allergen challenge during 42 positive ILNRs (open squares) and 42 phosphate-buffered saline (PBS) control tests (asterisks). B, The mean values of middle ear pressure were recorded during 42 positive ILNRs (open squares indicate right ear; closed squares, left ear) and 42 PBS control tests (x marks indicate right ear; and asterisks, left ear). Abbreviations are explained in the legend to Figure 1.

delayed). Of the 44 NNRs, 9 were accompanied by significant changes in MEP values: 3 isolated immediate MERs ($P < .01$), 4 isolated late MERs ($P < .05$), and 2 dual late MERs ($P < .02$ for immediate and $P < .05$ for late). The remaining 47 MERs recorded during the 12 positive NRs and 35 NNRs did not display any significant changes in MEP values with respect to the PBS control tests ($P > .10$). No significant changes in the MEP values were recorded during the 173 PBS control tests ($P > .10$). The tympanometric compliance values at baseline (before allergen challenge) were low in all patients studied (range, 0.2–0.5 cm³; mean $\pm$ SE, 0.35 $\pm$ 0.07 cm³). During 85 of the 126 positive MERs and during 3 of the 47 negative MERs, the compliance values

decreased slightly (mean $\pm$ SE, 0.25 $\pm$ 0.05 cm³), whereas a slight increase in the compliance values (mean $\pm$ SE, 0.40 $\pm$ 0.05 cm³) was recorded during 6 of the 126 positive MERs. However, all these compliance changes were nonsignificant ($P > .05$). No significant differences were found in the MEP changes between the right and left MEs during the positive responses ($P > .05$), negative responses ($P > .10$), and PBS control tests ($P > .50$). The association of MERs with subjective complaints is presented in Table 2.

NRs and MERs in Control Subjects

The 42 control subjects developed 42 positive NRs to the repeated allergen challenge: 15 IINRs ($P < .01$), 16 ILNRs

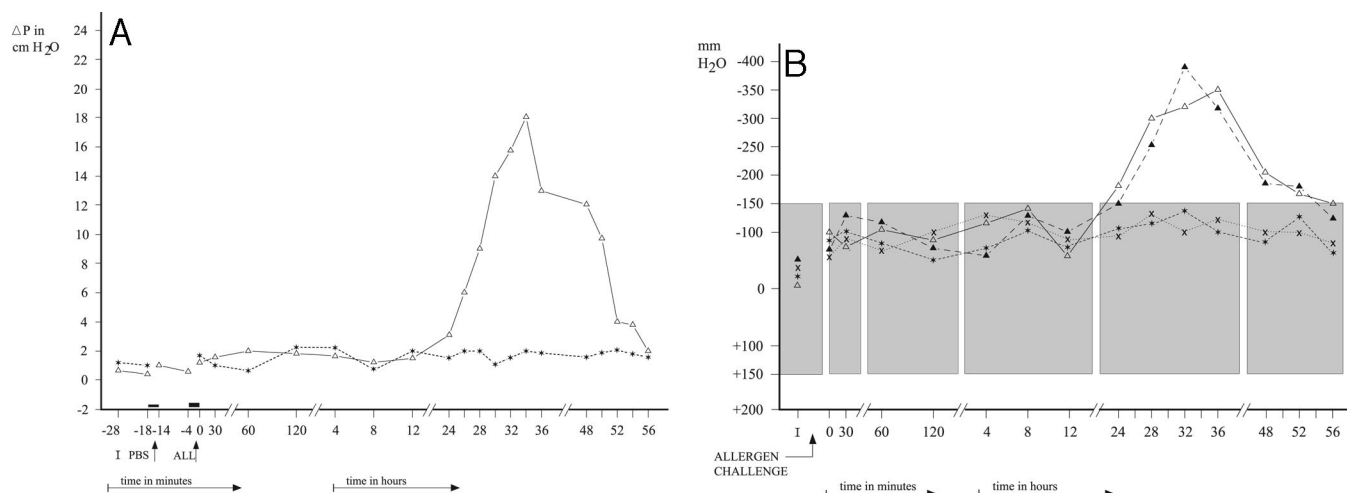


Figure 3. The isolated delayed nasal response (IDYNR) to allergen challenge (A) and the middle ear response accompanying the IDYNR (B). A, The mean nasopharynx-nostril pressure gradient values were recorded after the allergen challenge during 18 positive IDYNRs (open triangles) and 18 phosphate-buffered saline (PBS) control tests (asterisks). B, The mean values of middle ear pressure were recorded during the 18 positive IDYNRs (open triangles indicate right ear; closed triangles, left ear) and 18 PBS control tests (x marks indicate right ear; asterisks, left ear). Abbreviations are explained in the legend to Figure 1.

($P < .01$), 5 DLNRs (immediate plus late; $P < .05$), 5 IDYNRs ($P < .05$), and 1 DDYNR ($P < .05$). No significant differences were found between the first and the repeated NRs ($P > .20$). The MEP values before the nasal challenge with allergen at baseline were all within normal range in all control subjects. No significant changes in MEP values were recorded during all 42 repeated NRs ($P > .10$).

DISCUSSION

The pathogenesis of chronic SOM is clearly related to the abnormal function (dysfunction) of the ET.^{1-5,10-12,14,21-23} The ET facilitates the communication of the ME with the nasopharynx, with the nasal cavity, and also indirectly with the paranasal sinuses. In this way, the ET may play an important role in some disorders of the ME.^{2-4,21-23} The ET performs 3 basic functions: (1) protection of the ME from the nasopharyngeal secretions and sound pressure; (2) drainage of the ME secretions into the nasopharynx; and (3) ventilation of the ME cavity, which serves to equilibrate the air pressure in the ME with the atmospheric pressure, to replenish oxygen that has been absorbed, and to allow the escape of the gases produced in the ME cavity.^{1-5,9} The abnormal ET functions that may contribute to the development of chronic SOM are its obstruction, abnormal patency, and nonoptimally functioning ciliated epithelium lining the ET.^{1,3,5}

The role of allergy in the pathogenesis of chronic SOM has already been discussed in the literature.^{1-5,7-9,13-23,25-27} The allergy can be involved in chronic SOM by various mechanisms: (1) the allergic reaction (the antigen-antibody interaction with subsequent steps) can take place primarily in the mucosal membrane of the ET and/or ME cavity; (2) the allergic reaction occurs in the mucosal membrane of the nasopharynx and/or its related structures, such as the lym-

phatic or adenoid tissue, and the released mediators have a secondary effect on the peritubal and tubal mucosa of the ET, with subsequent progression into the ME cavity; and (3) the allergic reaction occurs primarily in the nasal mucosa. This reaction leads to the release of various mediators and relevant immunologic factors, which may then migrate into the nasal secretions and be transported to the nasopharyngeal ET orifice or the released mediators cause the primary NR (nasal mucosal edema and hypersecretion), resulting in nasal obstruction. The nasal mucosal edema can affect the ET in 2 ways, either extending directly to the nasopharyngeal ET orifice or through nasal obstruction. Nasal obstruction can then lead to an increase in the negative pressure in the nasopharynx, resulting secondarily in decreased patency of the ET, disturbance of its ciliary epithelium function, and an ET obstruction, with a subsequent increase in the negative pressure in the ME cavity. This process causes an accumulation of the secretions and gases in the ME cavity, with subsequent thickening of the ME mucosa, due to edema and/or infiltration, and changes in ME function. However, under some circumstances, the nasal obstruction can also lead to an increase in the positive nasopharyngeal pressure, causing aspiration of nasopharyngeal secretions into the ET and ME cavity and positive pressure in the ME.^{1-9,14,21-27} The most serious consequences of chronic SOM may be decreased eardrum elasticity, the appearance of fibrotic changes, and hearing impairment.^{1-10,29-31} Nevertheless, there is a dearth of information concerning the conditions allowing nasal allergy to induce chronic SOM in some patients, whereas it does not influence the ET and ME in others. Another still unanswered question concerns the mode of the nasal allergy involvement in ET dysfunction. Is this process realized predominantly through the primary nasal mucosal edema with subsequent

nasal obstruction or through the released mediators directly affecting the nasopharyngeal ET orifice or it is a combination of both of these mechanisms? Our findings would suggest the possible involvement of both the mechanisms. The many NRs were accompanied by MEP changes, indicating the involvement of nasal mucosal edema in ET dysfunction. The tympanometric changes, an increased MEP negativity with slightly decreased compliance, may correspond with a combination of the types B and C tympanograms.^{29–38} However, the arbitrary classification of the particular tympanogram types, described in the literature,^{32–34} may be disputable because the existence of various transient subtypes of tympanogram has been reported.^{35–38} The appearance of MEP changes during some NNRs (ie, in the absence of nasal mucosal edema) cannot be explained satisfactorily. The data of this study do not allow any conclusion about whether or not released mediators directly affected the ET and ME functions without causing any edema of the nasal mucosa, because no mediators were measured in the nasal secretions during this study. The lack of significant MEP changes during the NPTs in control subjects would not confirm some other researchers' findings of the ET obstruction due to the nasal challenge with allergen in subjects with allergic rhinitis but without ME disease.²² Another interesting observation in this study was the recording of 28 NNRs and negative MERs in patients with chronic SOM. This finding may probably be explained by either the possible involvement of other allergens, different from the allergens tested, or an allergic reaction taking place on a site different from the nasal mucosa (eg, nasopharynx or directly in the ET). Nevertheless, more concurrent research will be needed to clarify the previously mentioned questions. The diagnostic confirmation of the involvement of allergy in ET dysfunction and the pathogenesis of chronic SOM is not an easy issue. The skin tests and RAST have advantages and disadvantages.²⁷ They can easily be performed, and the results are quickly available. However, they provide evidence of the existence of an allergy component elsewhere in the body that cannot be related directly to any particular organ or tissue. These tests are performed on one organ, and their results cannot be applied indiscriminately to other organs. Furthermore, they did not provide any evidence of local antibodies in the mucosal membranes of other organs.²⁷ The serum RAST concerns the IgE antibody only, and it does not provide any evidence of the involvement of antibody of other classes. Finally, these tests are performed as a single measurement and they do not reveal any information on the dynamic involvement of the hypersensitivity mechanism(s).^{26–28}

From this viewpoint, the nasal challenge with allergen, in combination with the recording of variables indicative for ET and ME functions and their changes (eg, tympanometry), is a suitable method for the confirmation of the causal involvement of a certain allergen in the nasal mucosa and in ET and ME complaints, resulting in the appearance of a certain type of response, which can be quantitatively recorded during its dynamic course.^{25–27} Although the NPTs are laborious and

time consuming and require special equipment and facilities, they generate important clinical data that cannot be gathered by other diagnostic tests.^{25–28}

By combining the recorded variables, it is possible to confirm a causal role of one organ in a response of another organ, in this case the role of the nasal mucosa in the ET and ME. In addition, the significant correlation of the first and repeated NPTs in the control subjects would confirm reliable reproducibility of the NPT.^{25–28}

The NPTs can also discriminate the participation of the allergy component and the nonspecific hyperreactivity in the patient's complaints.²⁷ Another important advantage of the NPTs is their ability to follow the relative values of the variables, comparing prechallenge with postchallenge data. In this way, the NPTs are not dependent on the absolute variable values, which may display high variations.²⁸ Our results emphasize some important clinical implications. Chronic SOM, due to ET dysfunction caused by allergy, can occur in adults more frequently than is usually expected in practice. The involvement of various hypersensitivity mechanisms may result in the appearance of 3 basic types of MERs, analogous to the 3 basic types of NRs.^{26,27} The NPTs with allergens performed by rhinomanometry in combination with tympanometry may be a useful diagnostic tool in patients with chronic SOM, also having an important impact on the therapeutic management of this disorder.

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