

Monitoring methods for local nasal immunotherapy

Passali D, Bellussi L. Monitoring methods for local nasal immunotherapy. Allergy 1997; 52(suppl 33): 22-25. © Munksgaard 1997.

D. Passali, L. Bellussi

ENT Clinic, University of Siena Medical School,
Siena, Italy

When a patient is affected by specific vasomotor rhinopathy (allergic rhinitis), both perennial and seasonal, all the nasal functions are altered to various degrees. For this reason, in the evaluation of the efficacy of an antiallergic therapy we include: 1) anterior rhinoscopy; 2) active anterior rhinomanometry; 3) positioned acoustic rhinometry; 4) determination of mucociliary transport time; and 5) specific nasal provocation test. Active anterior rhinomanometry performed according to the directions of the International Committee on Standardization allows reliable assessment of the nasal respiratory function. Acoustic rhinometry is an objective method to assess the geometry of nasal cavities but, as a new method, needs more standardization with particular care in connecting the nose-piece to the nostril. Both these tests performed before and after local administration of nasal decongestants allow quantification of the congestion degree of the nasal mucosa. Determination of mucociliary transport time, according to the method of coloured tracer, is easy to perform and may be considered a reliable indicator of the mucosa eutrophism. In our clinical experience we have often found mucociliary transport times delayed or even blocked, especially in patients affected by perennial allergic rhinitis. According to our experience the specific nasal provocation test is one of the most important tests in this field: it is more sensitive than skin tests and RAST in the asymptomatic phase and it is able to show organ allergies. In this paper we review the importance of this test, the methodology we currently use as well as changes after local nasal immunotherapy.

Key words: active anterior rhinomanometry; acoustic rhinometry; muco-ciliary transport time; specific nasal provocation test.

D. Passali
ENT Clinic
University of Siena Medical School
Siena
Italy

It is well known that breathing through the nose is the only physiological form of breathing. It is perhaps less known that the act of breathing, apparently so simple and natural, presupposes the presence of a normally shaped anatomical structure and a healthy nasal mucosa. The nasal mucosa effects a complex action of filtration, humidification, heating and defence on the air breathed in, aimed at making it suitable for the gaseous exchanges which take place at alveolar level. Non-physiological breathing through the mouth causes not only hyposmia or anosmia of mechanical type, but also a loss of the functions of defence and, as a consequence, the extension of the phlogoses to the sinuses, the middle ear and the lower airways.

Organic alterations are often combined with psychic and behavioural disturbances; in childhood bradypsychism prevails: the child is absent-minded, indifferent to his environment and finds difficulty in concentrating. The main psychic symptoms in

adults affected by chronic respiratory insufficiency are irritability, irascibility, disturbance of sleep and, as a consequence, reduced working capacity.

Specific vasomotor rhinopathy or allergic rhinitis, either in the perennial or seasonal form, is characterized by the hyperreactivity of the mucosa of the upper respiratory tract to stimuli which are innocuous for the majority of people.

Allergic inflammation affects the neurovegetative system of nasal mucosa, leading to alterations of the regulating mechanisms of blood vessels repletion and the activity of glandular secretion. Symptomatology is characterized by nasal obstruction, rhinorrhoea, itching and sneezing which may be considered the epiphenomena of internal imbalance of the systems regulating nasal reactivity (1). The importance of correct clinical and therapeutical monitoring of allergic rhinitis is understandable in the light of the social and economic impact of this pathological entity.

The clinical phase of allergic rhinitis can start at every age but the highest incidence is found between 15 and 25 years. In children the beginning age is usually between 8 and 12 years (2). Regarding prevalence in relation to age and gender, this is higher in males before 18 years, after this age in females. The mean prevalence in different countries ranges from 6.3% in Israel to 15% in Denmark and Great Britain. It has been calculated that in this country 1 000 000 people turn to their physician for atopic problems.

From our recent epidemiological studies it has been found that in Italy the prevalence of vasomotor rhinopathy (both the aspecific and allergic form) is currently 20–25% in young adults and 3% of the elderly. The main causes of nasal allergy in Italy are represented by *Graminaceae* (36%), *Dermatophagoides* (33%) and *Parietaria* (12%), with a high incidence of mixed forms (3).

Allergic rhinitis is increasing in every country. The main reasons for increasing prevalence are: transfer of people from rural to urban areas, pollution and cigarette smoke and conditioning systems of houses. All these factors can affect the nasal mucosa in an aspecific manner, leading to alterations of its reactivity and permeability; as a consequence they open the way to specific allergens in predisposed subjects. This is the "priming effect" marked by Connell (1968) (4).

In the light of these considerations it seems evident that every rhinologic centre needs specific tools for the diagnosis and therapeutical monitoring of allergic rhinopathies.

Clinical data

Recording the symptoms does not supply enough data to characterize allergic rhinitis from an aetiological point of view. Itching, sneezing, rhinorrhoea and congestion are "standard" forms of defence of the nasal mucosa against specific and aspecific noxae. More meaningful information is drawn out from the conditions under which the symptomatology appears: whether it is seasonal or not, its correlation with the more common inhaled allergens, the presence of familiarity. Before starting with specific allergologic procedures, an examination of whole nasal functionality must be performed.

Rhinomanometry

Rhinoreomanometry (5, 6) performed according to the rules suggested by the Committee on Standardization, gives important information on the respiratory function of the nose, the key of the physiology not only of the nose, but of the entire

rhino-pharyngo-tubal district. When anterior rhinomanometric examination reveals lower than normal values for nasal conductance, we carry out the nasal decongestion test. If this test proves negative, one might envisage the possibility of a surgical correction of the pathology already revealed in the course of objective examination and confirmed by RX examination. On the contrary, an even partial improvement of perviousness suggests involvement of the mucosa in the pathological picture, as it occurs in allergic rhinopathy.

Acoustic rhinometry

Acoustic rhinometry is a relatively new method of using acoustic reflections from the airway to estimate their shape and the morphological changes induced by the congestion of the mucosa. By comparing the acoustic wave reflected from the nasal cavity to the incident wave this technique makes it possible to measure the cross-section in fixed area at varying distances from the nostril (such as, for example, at the level of the head of inferior turbinate). The reactivity of the mucosa to the administration of nasal decongestant is documented by changes in the profile of the acoustic rhinogram (7, 8).

Nevertheless this method, as a new method, needs more standardization such as the choice of the most suitable acoustic wave (white noise is preferable to clicks at different frequencies), the method of connecting the nose-piece to the nostril or the positioning of the head in respect to the incident wave. In diagnosis and follow-up of anti-allergic therapies we perform acoustic rhinometry with the aid of an optometric craniostat.

Determination of muco-ciliary transport time

The degree of involvement of the nasal mucosa in allergic reactions is also well documented by determination of the efficiency of nasal mucociliary transport. Nasal mucociliary function is one of the most important and indispensable mechanisms of the airways against environmental pollution: it is governed by cilia, mucus and the interaction between them. Their functional and/or structural impairment is responsible for mucociliary dysfunction.

In seasonal forms of allergic rhinopathies, as a consequence of increased glandular secretion the ratio between the sol and gel phase of the mucus is altered and the efficiency of muco-ciliary clearance is impaired. In perennial form, allergic inflammation may be responsible for more important alterations, to the ciliar structure or for the metaplastic transformation of the respiratory mucosa

into squamous epithelium. In our experience we have found delayed times in seasonal forms and blocked times (more than 30 min in perennial forms) (9). In performing determination of nasal muco-ciliary transport time, we use a mixture of charcoal powder and 3% saccharine; charcoal powder is an insoluble tracer and it is used for monitoring the transport efficiency of the particles entrapped into the outer gel layer; saccharine is a soluble marker, and gives us the times of clearance into the inner sol layer (10).

Allergy tests

From an allergologic point of view the identification of aetiological factors is extremely important, not only as it confirms the clinical diagnosis but also to carry out targeted preventive and therapeutic measures. It is carried out according to a precise sequence. We can distinguish:

- First level investigations (skin tests);
- Second level investigations (serum tests for specific IgE); and
- Third level investigations (elimination and provocation tests) (11).

If the skin tests are carried out properly and interpreted correctly, and used together with information from the patient's history and clinical data, it is possible to identify the responsible allergen in the majority of cases.

In the case of specific vasomotor rhinopathy, mediated by hypersensitivity reactions of the first type, the prick test can be used. Tests by intradermic injection are more sensitive but less specific, and they carry a higher risk of systemic reactions in relation both to the higher dosage and to the method of administration. In the majority of patients the prick test, easily reproduced, fairly specific and easy to carry out, is able to give sufficient information in clarification of the aetiological diagnosis.

Nevertheless, in some subjects negative results of the skin tests contrast with anamnesis, which testifies in favour of an allergic form. In this case it is necessary to perform second and/or third level investigations.

Considering *in vitro* tests, total IgE dosage (PRIST or ELISA) in the serum is not reliable: even though we frequently come across higher average rates of total IgE in allergic subjects in comparison to controls, the wide dispersion of the values implies an unacceptable level of uncertainty in the interpretation of the results. Total IgE dosage in nasal secretion shows higher significance, but the absence of standardization and universally accepted reference for nasal lavages limits application of this method.

Currently, the most significant laboratory test is the specific IgE dosage (RAST or ELISA) both in serum and nasal secretion. It is well correlated with the condition of allergic rhinopathy and is a useful aid in the case of risk of systemic reactions or in the presence of skin disease that can influence cutaneous reactions. Their high cost and lower sensitivity in comparison to *in vivo* tests are the main limitations of these methods.

Third level investigations, in our case the nasal specific provocation test, have their rationale in the pathogenic mechanism of sensitization. The clinical symptoms of allergic rhinitis depend on the prevalent or exclusive localization of the previously "primed" mastocytes in the organ of shock. In other words, in specific vasomotor rhinopathy the nose is the meeting point of the allergens and specific IgE: it is here that the greater part of reagins are concentrated. The surplus circulates in the bloodstream and colonizes distant areas with a high content of mastocytes, such as the skin. Proposed and carried out for over a century now, the nasal provocation test can be considered, at least from a theoretical point of view, as the most correct and direct aetiological and quantitative method for the diagnosis and monitoring of allergic rhinopathy. This test, in principle valid, has always met serious obstacles in its practical application: the main limitations lie in the means of administration of the allergen and the preselected parameters for the evaluation of the response (12). Present-day techniques have the goal of guaranteeing uniform distribution without provoking physical or mechanical stimulation of the nasal mucosa.

Atomiser-dosimeters, which deliver a known quantity of solution, or simple devices that release powder containing the lyophilized extracts dispersed in lactose, are therefore to be preferred. It has been demonstrated that using allergen extract in "macronized" powder form lends clinical efficacy and safety to the treatment because of the stability and standardized dosage of the allergen. The use of the powder form avoids problems associated with the preparations consisting of aqueous solution administered into the nostril by means of squeeze bottles: (1) poor stability as a result of container absorption and decomposition; and (2) difficulty in administering an exact amount of allergen (it is impossible to use metered-dose inhalers because of chemical incompatibility between the aqueous solution and propellant).

Certain sophisticated apparatus that can create dispersion of the allergen in the environment that is similar to physiological dispersion (13) or quantification of the erogated allergen are interesting in terms of clinical research but without possibility of practical application. Regarding the choice of

criteria for evaluation of the test the registration of appropriately quantified clinical symptoms (itchiness, sneezing, rhinorrhoea, nasal obstruction, tearing, conjunctive hyperaemia) is usefully integrated by the measurement of nasal patency in relation to stimulation with increasing doses of allergen.

The present availability of computerized rhinomanometric apparatus, which provides for the use of total facial masks, has made it possible to reach high levels of reliability and reproduction and to overcome problems related to air escaping from the receivers and deformation of the nasal valve. Thus measurement of the partial and total resistances that the air flow encounters in inhalation and exhalation at the level of the upper airways constitutes an indispensable parameter for the objective evaluation of the reactivity of the organ to a specific allergen. Also, recording the acoustic rhinogram after provocation is a quicker method of monitoring reactive congestion of the nasal mucosa at the level of the head of inferior turbinate. Nevertheless, we must always consider problems related to the particular care we must take in positioning the head of the patients in respect to the incident acoustic wave. The most complete mode of execution and interpretation of the NPT is performed, in our opinion, according to the following steps:

- 1) Basal active anterior rhinomanometry (AAR) in order to exclude a respiratory stenosis incompatible with the test;
- 2) Insufflation of lactose into the nasal fossa which shows the lowest resistance and, after waiting 10 min, control AAR (these results are considered to be the reference values);
- 3) Administration into the same fossa of the powder containing the lyophilized allergen at lowest concentration (2.5 AU) and AAR repeated after 10–15 min. If the resistances do not change, a higher concentration is tried and one continues in the same way with increasingly higher concentrations (5, 10, 20, 40, 60, 80 AU). The NPT is considered positive when there is an increase in resistance equal to or greater than 100%.

Conclusion

Allergic rhinitis is not a life-threatening disease, but its social impact is remarkable, its prevalence being over 10% of the total population all over the world. At the same time prevalence is increasing

because of changes in life-style, indoor as well outdoor pollution and stress. The efficacy of LNIT in the treatment of allergic rhinitis has been well documented in the last decades; nevertheless, on the basis of our experience in the rhinological field we are convinced that a correct diagnosis of nasal allergy must include from some instrumental tests aimed at monitoring the degree of alteration of all the nasal functions (respiratory, specific and aspecific defence) and at recognizing the nose as the shock organ of the allergic reaction. This last is the task of the specific NPT: it is the most suitable means to establish, in polysensitive subjects, the prevalent allergen at nasal level, or to quantify the threshold of sensitization. This is necessary before starting a specific immunotherapy, and during such therapy for monitoring the degree of desensitization.

References

1. Anggard A. Specific and non specific nasal hyperreactivity. In: Passali D, editor. *Around the nose*. Conti Tipocolor, Firenze, 1988:45-54.
2. Passali D. Allergy in Childhood. *Rhinology* 1986;24:25-8.
3. Passali D. Screening of allergy rhinitis. *Rhinology* 1983; 21:321-8.
4. Connell JT. Quantitative intranasal pollen challenge II. Effect of daily pollen challenge, environmental pollen exposure and placebo challenge in nasal membrane. *J Allergy* 1968;41:153-7.
5. Clement PAR. Committee report on standardization of rhinomanometry. *Rhinology* 1984;22:151-3.
6. Clement PAR. Rhinomanometry. *Rhinology* 1991; Suppl 14.
7. Grymer LF, Hilberg O, Elbron O, Pedersen OF. Acoustic rhinometry: evaluation of the nasal cavity with septal deviations, before and after septoplasty. *Laryngoscope* 1989;99:1180-83.
8. Grymer LF, Hilberg O, Pedersen OF, Rasmussen TR. Acoustic rhinometry; values from adults with subjects with free nasal patency. *Rhinology* 1991;29:35-40.
9. Passali D, Bianchini Ciampoli M. Normal values of mucociliary transport time in young subjects. *Int J Pediat ORL* 1985;9:151-6.
10. Passali D, Bellusi L, Bianchini Ciampoli M, De Seta E. Our experience in nasal mucociliary transport time determination. *Acta ORL Scand* 1984;97:319-23.
11. Errigo E. Il memorandum della S.I.A.I.C sulla diagnostica delle allergopatie. In: Pallesstrini E, Passali D. editors. *Allergie in otorinolaringoiatria: tecniche diagnostiche e terapeutiche*. Scuola Sup. di Oncologia e Scienze Biomediche. Genova, 1992:19-24.
12. Bellusi L. I test di provocazione nasale. In: Pallesstrini E, Passali D, editors. *Allergie in otorinolaringoiatria: tecniche diagnostiche e terapeutiche*. Scuola Sup. di Oncologia e Scienze Biomediche. Genova, 1992:123-33.
13. Mock DC. A controlled evaluation of two anti-histamine compounds using nasal engorgement as an index of response. *J Allergy* 1963;34:432-5.