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Allergic and nonallergic rhinitis and skin sensitization to metals: is there a link?

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Summary

Background. Chromium, Cobalt and Nickel are responsible for contact dermatitis, that is largely prevalent in the general population. They can act also as irritants in the upper and lower respiratory airways. Also rhinitis (allergic and nonallergic) is a high prevalence disorder. Both diseases could share some common inflammatory mechanisms, but the clinical association between skin sensitization to metals and rhinitis was never studied. **Objective.** We assessed the presence of skin sensitization to metals in subjects with rhinitis. **Methods.** Patients suffering from rhinitis underwent a standard diagnostic procedure, including skin testing, nasal endoscopy and nasal cytology. Control healthy subjects were also included. None of the patients had skin diseases. All subjects underwent patch test with Chromium, Cobalt and Nickel. **Results.** None of the 26 controls had positive skin prick test or nasal cytology. The 82 rhinitis patients were subdivided into allergic (group A = 27), nonallergic (group B = 31) and overlapping (group C = 24). The prevalence of positive patch test to metals was 26% in group A, 45% in group B, 42% in group C and 31% in controls. The percentage of patch-positive subjects was significantly different between Group A and B ($p = 0.0045$; OR: 0.43), Group A and C ($p = 0.0186$; OR: 0.49), and Group B and controls ($p = 0.0360$; OR: 1.85). There was a significant difference between groups A + controls and B + C. **Conclusion.** Even in the absence of skin diseases, the prevalence of sensitization to metals (patch test) is greater in nonallergic and overlapping rhinitis, as compared to allergic rhinitis and controls.

Introduction

Chromium (Cr), Cobalt (Co), Nickel (Ni) and their salts are the metals most frequently responsible for contact dermatitis (CD). The trivial definition of contact “allergic” dermatitis mainly relies on historical bases, but the mechanisms of CD are not IgE-mediated, and rather involve a delayed T-cell inflammation. In Europe, the prevalence of CD due to Ni, Co and Cr is estimated around 20%, 7% and 4%, respectively. Of note, Italy seems to have the higher prevalence of CD (around 32%) (1), similar to that reported in the USA (2,3). The occurrence of CD is most frequent in women, since Ni and Co are largely

used in jewellery and cosmetic products (4). On the other hand, Cr-related CD is observed more frequently in men, due to occupational exposure (5).

Such metals can act also on the respiratory mucosae, especially in the nose, where they can induce an irritative or vasomotor rhinitis (6). As a matter of fact, both rhinitis and CD are high prevalence diseases and share an inflammation-driven mechanism (mainly Th2 and IgE-mediated in allergic rhinitis, cell-mediated in CD and largely unknown in nonallergic rhinitis). Nonetheless, nothing is known about the possible relationship between rhinitis (either allergic or nonallergic) and skin

sensitization to metals. Thus, we attempted to evaluate if some relationship exists between these two diseases (CD and rhinitis), based on clinical and biological observations.

Methods

Consecutive adult and adolescent subjects, referred to our Unit for rhinitis symptoms between October 2014 and April 2015, were evaluated. The patients underwent a standard diagnostic work-up, including allergy diagnosis, nasal endoscopy and nasal cytology. In addition, all of them underwent a patch test procedure to assess the presence of skin sensitisation to Ni, Co and Cr. Patients with mechanical / anatomical nasal abnormalities (polyposis, rhinosinusitis, turbinate hypertrophy) were not included. According to the clinical and biological characteristics of rhinitis, patients were subdivided into 3 groups: A = allergic rhinitis (at least one skin prick test, SPT, positive); B = non-allergic rhinitis (nasal inflammation with negative SPT); C = overlapping rhinitis (positive SPT and discordant nasal cellular profile). A group of healthy subjects, without nasal symptoms and with negative tests was also included. None of the enrolled subjects had clinical or historical evidence of skin diseases. All patients (or their legal caregiver) provided an informed consent. The study was approved by Inner Ethical Committee of Bari University.

Clinical evaluation. After collecting the personal data into a dedicated database, all subjects underwent a detailed clinical histo-

ry, including family history, duration of symptoms, seasonality, comorbidities (e.g. asthma, polyposis, systemic diseases, malignancies) according to guidelines (7). An external inspection of the nose and conjunctiva was carried out to exclude gross abnormalities, and a general clinical visit was performed, where vital parameters were recorded.

Nasal endoscopy. It was carried out with a 3.4 mm diameter flexible nasal endoscope (Vision-Sciences® ENT-2000), to assess the presence of major abnormalities, such as septal deviation, polyposis, turbinate hypertrophy, or exudation from the ostiomeatal complex.

Nasal cytology. This procedure was performed by scraping the middle part of the inferior turbinate with a Rhino-Probe® device (Arlington Scientific). The sample was smeared on a slide, air-dried, then stained with the May-Grünwald Giemsa preparation. Type and cell number were examined using microscopy (Nikon® E600). Cell types were identified, and intracellular components were studied at x 1000 in oil immersion. The mean number per 50 fields was calculated and reported (8,9).

Skin prick test. It was performed and read according to the recommendations of the European Academy of Allergy and Clinical Immunology (10). A standard panel with the most common aeroallergens (Stallergenes, Milan, Italy) was used: house dust mite, grass mix, parietaria, olive, cypress, compositae mix, alternaria, ragweed, cat and dog dander.

Patch test. It was performed according to guidelines of the European Society of Contact Dermatitis. Four substances were ap-

Table 1 - Demographic, clinical and cytological characteristics of the studied population.

| | Group A (n = 27) | Group B (n = 31) | Group C (n = 24) | Group D (n = 26) |
|---------------------------------|------------------|------------------|------------------|------------------|
| Mean age (years) | 35.1 | 47 | 35.5 | 41.1 |
| Age range (years) | 16-67 | 23-80 | 15-68 | 17-66 |
| M/F | 12/15 | 13/18 | 10/14 | 5/21 |
| Moderate / severe rhinitis | 25/27 | 31/31 | 22/24 | 0 |
| 2 or more positive skin test, N | 22 | 0 | 12 | 0 |
| Monosensitized, N (%) | 5 (19) | 0 | 12 (54) | 0 |
| Nasal cytology ¹ | | | | |
| Neutrophils | 10.4 (33.8) | 20.6 (41) | 22.4 (49.7) | 2 (6.7) |
| Eosinophils | 4.2 (8.8) | 9.7 (11.6) | 11.3 (11.5) | 0 |
| Lymphocytes | 0.3 (1.5) | 0.6 (3.7) | 0.7 (2.3) | 0 |
| Mast cell | 1.1 (4.2) | 5.3 (11.4) | 6.5 (7.5) | 0 |
| Any patch test positive | 7 (26%) | 14 (45%) | 10 (42%) | 8 (31%) |
| Ni | 5 | 12 | 5 | 4 |
| Co | 4 | 4 | 8 | 7 |
| Cr | 2 | 1 | 1 | 0 |

¹Mean cell count on 50 fields (SD)

plied: Nickel sulphate esahydrate 5%, Cobalt II sulphate 2.5%, Chromium sulphate 0.5% and white petrolatum as negative control. The results were read 48 hours after the application of the test (11).

Statistical analysis. The Chi-square test was applied to the parameters considered, to identify the differences among groups.

Results

Eighty-two patients (35 male, mean age 41 years, age range 15-80 years), were studied at our Unit between October 2014 and April 2015. All of them suffered from rhinitis symptoms (moderate / severe in 78/82), whereas the healthy control group included 26 patients (5 male, mean age 41 years, age range 17-66 years). No difference in the severity of the disease could be detected among groups. The demographic and clinical characteristics are summarized in **table 1**.

According to the results of the diagnostic work-up, 27 patients (32.9%) had allergic rhinitis (**Group A**) (5 monosensitized), 31 (37.8%) had non-allergic rhinitis (**Group B**) with various cytological profiles: 17 non-allergic rhinitis with eosinophils (NARES); 4 non-allergic rhinitis with mast cells (NARMA); 10 non-allergic rhinitis with eosinophils and mast cells (NARES-MA) (12-14). Finally, 24 patients (29.3%) had an overlapping rhinitis (group C), that is with allergic sensitizations and a cellular profile typical of vasomotor rhinitis (**Group C**): 7 NARES, 4 NARMA and 13 NARESMA (15). Obviously, all the 26 patients in the control group (**Group D**), had no symptoms of rhinitis, negative skin test and negative nasal cytology.

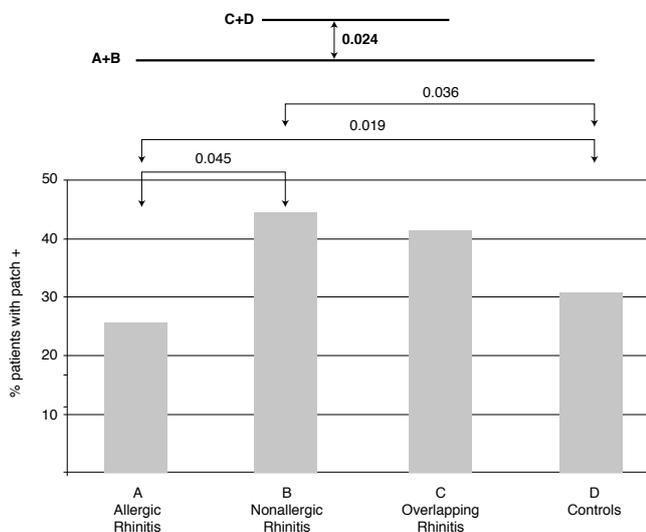
A patch test positivity (to one or more of the tested metals) was found in 7/27 patients in group A, in 14/31 in group B, in 10/24 in group C and in 8/26 in the control group. A significant difference in the percentage of patch-positive subjects was found between Group A and B ($p = 0.0045$; OR: 0.43), Group A and C ($p = 0.0186$; OR: 0.49), and Group B and D ($p = 0.0360$; OR: 1,85) (**figure 1**). Also, there was a significant difference between groups A + D and B + C ($p = 0.0239$; OR: 1.96). Notably, there was no detectable exposure to metals, according to clinical history and demography among groups.

Discussion

Some metals are largely present in our life, as components of foods and beverages (e.g. canned meat, vegetables or shellfish), or used in jewellery, or in various occupational fields. In fact, Ni is responsible for a number of cases of CD, greater than those caused by all other metals, as testified by the abundant literature. The occurrence of CD is increasing in adolescents, probably in relation to the use of metal-containing devices or ornaments (16). Despite often including the term "allergic", CD is not IgE-mediated, but a type 4 cell-mediated immunological disease. It appears as an eczema (primary eruption) that is well confined to the skin areas which are in contact with the metal containing objects: ear lobes (earrings), wrists (bracelets), neck (chains), umbilical region (buttons). Metal allergy may also be present in systemic forms (secondary eruptions) that appear at sites different from those that are in contact with the metal (17) or, at least for Ni, with extra-cutaneous systemic manifestations, such as the Systemic Nickel Allergy Syndrome, with respiratory symptoms (18,19). In addition, some investigators suggested the possibility of a toxic effect on respiratory mucosae following a prolonged exposure: respiratory mucositis, vasomotor rhinitis, occupational asthma (20-25). Of note, an increased rate of sensitisation to metals was previously reported in asthmatic patients (26). Nonetheless, there is scarce information on the possible relationship between non-occupational exposure to Ni, Cr or Co and respiratory diseases, although it is conceivable that the pathophysiological mechanism are in part similar, due to the involvement of the adaptive arm of immunity response, as demonstrated in asthma (27). The use of nasal cytology allows to better distinguish the "vasomotor" rhinitis, characterized by an intense cellular infiltration (NARES, NARMA, NARES-MA), from the classic allergic rhinitis and from the overlapping forms (28).

According to the results of our study, it seems that the cutaneous sensitization to metals is less frequent in patients with allergic rhinitis, and more prevalent in those with non-allergic rhinitis or overlapping disease (as confirmed by the sums of group A+D and C+D). Indeed, we could not provide a pathophysiological explanation, and simply we described a phenomenon, that was

Figure 1 - Percentage of patients with a positive patch test in each group. The significant differences are indicated above the bars.



not investigated before. Nonetheless, it is conceivable that the association of metal sensitisation and nonallergic rhinitis is not simply “by chance”, and would deserve further investigations.

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