

REVIEW

ARTICOLO DI AGGIORNAMENTO

Systemic nickel allergy syndrome: an update

Sindrome sistemica da allergia a nichel: recenti acquisizioni

M.C. TURI, F. DI CLAUDIO, C. SCHIAVONE, N. VERNA, A. PERRONE, E. CAVALLUCCI, M. DI GIOACCHINO
Allergy Related Disease Unit, "G. d'Annunzio" University Foundation, Chieti, Italy

Key words

Nickel • Allergic Contact Dermatitis • Systemic Nickel Allergy Syndrome • Cytokines • Lymphocyte • NK cells

Parole chiave

Nichel • Dermatite allergica da contatto • Sindrome sistemica da allergia al nichel • Citochine • Linfociti • Cellule NK

Summary

Nickel is the metal that most frequently causes allergic reactions since it is an ubiquitous metal that can be found in many objects and foods. The major manifestations of nickel allergy are Allergic contact dermatitis and Systemic Nickel Allergy Syndrome (also called Systemic Contact Dermatitis – SCD). Clinically Systemic Nickel Allergy Syndrome is characterized by eczema, urticaria, flare up of previous positive patch tests and other skin manifestations, abdominal pain, diarrhoea or constipation, and other minor symptoms appearing after ingestion of nickel with food. The syndrome can be observed in vivo after oral provocation test. Many Authors administer for this purpose 0.3 to 10 mg Ni and the subsequent syndrome seems correlated to the amount of nickel administered. There are no specific laboratory data so the oral challenge is the gold standard in the diagnosis. The patho-physiology of Systemic Nickel Allergy Syndrome is quite different from the Ni-allergic contact dermatitis. In fact, Systemic Nickel Allergy Syndrome is characterized by a significant increase of IL-5 and IL-2 serum levels after challenges. It has been observed also modification in the CD expression in lymphocytes of Systemic Nickel Allergy Syndrome patients respect to the Allergic contact dermatitis patients and healthy controls both in the blood and in the gastrointestinal mucosa. All findings suggest a role of the Th2-type immune response in this syndrome.

Riassunto

Il nichel è il metallo che più frequentemente causa reazioni allergiche, poiché si tratta di un metallo ubiquitario presente in molti oggetti ed alimenti. Le principali manifestazioni di allergia al nichel sono la dermatite allergica da contatto e la Sindrome Sistemica da Allergia al Nichel (chiamata anche dermatite sistemica da contatto – SCD). La Sindrome Sistemica da Allergia al Nichel clinicamente è caratterizzata da eczema, orticaria, flare-up di precedenti patch test risultati positivi ed altri sintomi cutanei, dolore addominale, diarrea o stitichezza ed altri sintomi minori che compaiono dopo l'ingestione di nichel. Tale sintomatologia può essere evocata in vivo con il test di provocazione orale. Molti Autori descrivono la comparsa della sintomatologia nei pazienti allergici al nichel in seguito alla somministrazione di nichel da 0,3 a 10 mg. Non esistono esami di laboratorio specifici per la diagnosi di Sindrome Sistemica da Allergia al Nichel, pertanto, la provocazione orale con nichel rimane il gold standard nella diagnosi di tale patologia. Dal punto di vista patogenetico, la Sindrome Sistemica da Allergia al Nichel è molto diversa dalla dermatite da contatto da nichel; in particolare, nei pazienti affetti da Sindrome Sistemica da Allergia al Nichel si è osservato un significativo incremento dei livelli sierici di IL-5 e IL-2 dopo test di provocazione orale. Sono state osservate, inoltre, modificazioni nell'espressione delle molecole CD sui linfociti sia nel sangue che nella mucosa gastrointestinale di pazienti affetti da Sindrome Sistemica da Allergia al Nichel rispetto ai pazienti con dermatite allergica da contatto e controlli sani. Tutti i risultati suggeriscono come la risposta immunitaria di tipo Th2 svolga un ruolo fondamentale in questa sindrome.

Introduction

Nickel is a ubiquitous metal that can be found in many objects and foods. It represents the most common occupational, as well as public contact allergen. Sensitization to nickel can occur through different mechanisms: skin contact with nickel may induce allergic contact dermatitis (ACD); food ingested nickel

can cause gastrointestinal symptoms and/or chronic dermatopathies defining the Systemic Nickel Allergy Syndrome (SNAS) or Systemic Contact Dermatitis (SCD).

In the 1970s, some Authors¹ noted that many nickel-sensitive patients had cutaneous manifestations at a different site than those that have been in direct contact with nickel. This led to consider this manifesta-

tion a secondary type of eruption and a consequence of ingestion of nickel.

Systemic contact dermatitis is a term to define an inflammatory skin disease occasionally seen as a flare-up of a previous eczema or de-novo eczema similar to allergic contact dermatitis, when sensitive patients are exposed to nickel systemically².

The pathogenesis of the skin disorders is not completely known. The histopathology of the flare-up eczema in patients with systemic nickel allergy syndrome after oral nickel challenge is similar to the reactions in allergic contact dermatitis; but because SCD starts after a few hours or up to 1-2 following nickel ingestion, not only one type of hypersensitivity mechanism may be involved.

Nickel metabolism

Nickel blood concentrations vary greatly in different reports of oral challenge with the metal. It is known that many factors, including diet, stress, age and seasonal variation, may influence serum nickel levels. However, the most recent works show similar serum nickel concentrations in allergic patients and controls, both before and after metal ingestion.

Nickel is excreted equally well via urine and feces. Under normally dietary conditions 1-2% of ingested nickel is absorbed, and unabsorbed nickel is excreted with feces. In rats intravenously injected with nickel chloride 90% is eliminated in the urine within 4 days post-injection, and only 3% is excreted by fecal discharge³.

Nickel urinary excretion is rapid, no dose-dependent and its elimination appears to follow first-order kinetics⁴. Estimates of the half-life of urinary removal of nickel range from 20 to 60 h^{5,6}.

Nickel (Ni) absorption and/or excretion seem to be more elevated in atopic Ni-sensitized patients than in non-atopic patients. Urinary Ni excretion after ingestion of 1 mg of Ni sulphate is higher in Ni-sensitized atopic subjects than in Ni-sensitized non-atopic or non-allergic subjects⁷.

Serum and urine Ni of non-sensitized and Ni-sensitized women did not significantly differ. Serum and urine Ni levels determined before the oral Ni challenge were in the range of reference values recently reported by other Authors (0.2-2.0 µg/l of serum or urine). Ni was greatly augmented in urine and serum 4 h after the challenge (43-264 µg/l urine Ni and 15-52 µg/l serum Ni). 24 h after Ni ingestion, urine Ni was 41-153 µg/l and serum Ni 4-17 µg/l⁸.

Diet and *in vivo* challenges

Systemic contact dermatitis is seen when sensitized individuals are exposed to a hapten systemically, that is orally, trans-cutaneously, intravenously, subcutaneously, intramuscularly or by inhalation². Nickel is found in drinking water⁹ and many foods and its daily intake has been estimated between 200 and 600 µg; most ingested nickel remains unabsorbed within the gastrointestinal tract: only 1-10% is absorbed. In a healthy man, serum nickel concentrations vary from 1.6 to 7 µg/l and urinary nickel concentrations from 2 to 5 µg per day¹⁰. Continuous exposure to nickel might lead to oral tolerance mechanisms that modulate nickel sensitivity¹¹.

Patients with widespread, chronic, allergic-type dermatopathies and contact sensitization to nickel should be prescribed a low nickel diet, when a demonstrated dependence between diet and clinical manifestations is clear. Low nickel diet and a subsequent Ni oral exposure may be also useful in order to demonstrate the relationship between Ni ingestion and the appearance of symptoms.

Oral challenge experimental trials have been used to show that oral intake of nickel can elicit a systemic nickel allergy syndrome in nickel-sensitive individuals. The oral challenge was given in the morning at doses that vary from 0.3 to 10 mg. A definite dose-response reaction pattern to oral nickel exposure was observed among nickel-sensitive subjects¹². The Authors showed that the number of nickel-sensitive patients who reacted to oral exposure to 4.0 mg nickel is statistically significant more than those given a placebo. This was not the case for nickel-sensitive subjects who received 1.0 and 0.3 mg nickel. However, unequivocal cutaneous reactions were seen when nickel-sensitive patients were exposed to 1.0 and 0.3 mg nickel and to placebo, in addition to the nickel exposure from the normal dietary intake.

Reactions that occur in patients exposed to nickel include: itching, urticaria, oedema, eruptions of previously unaffected skin such as flexural dermatitis, a maculopapular rash and vasculitis-like lesions, flare-up reactions at previous sites of contact dermatitis, including the flare-up of current or former hand eczema and flare-up reactions of previously positive nickel patch tests; abdominal pain, diarrhoea and headache have also been described.

These tests were by no means dangerous for the patients' life and the trigger effects were generally limited to a more or less severe relapse of previous clinical manifestations.

The administration of nickel has been proposed also for treatment of such diseases^{13,14} and in no cases severe side effects have been reported.

The double-blind, placebo-controlled challenge test is the gold standard for this type of pathologies: therefore it is highly recommended and generally necessary for a correct diagnosis.

Experimental studies

In a previous study¹⁵ we examined blood and intestinal mucosa lymphocyte subpopulations as well as cytokine production in SNAS patients compared to healthy controls and patients suffering from ACD only. The study demonstrated a reduction of NK cell activity in sensitised patients in respect to the normal subjects (Fig. 1)¹⁶.

The normal lamina propria of gastrointestinal mucosa exhibit 60% of CD45RO+ T lymphocytes and 40% CD8+. In the gastrointestinal epithelium of allergic patients sensitive to oral nickel we found a lower infiltration of CD8+ lymphocytes as well as in skin biopsies from nickel patch test reactions. Furthermore, biopsies in nickel allergic subjects sensitive to food ingested nickel show higher levels of CD45RO+ cells in the lamina propria^{17,18}.

The exact role of specific cytokines in nickel allergy has not been elucidated in sufficient detail, but available published data do suggest its central role.

Patients how reacted to oral nickel exposure had a higher serum IL-2 and IL-5 before nickel challenge than healthy non-allergic controls and nickel-sensitive patients who did not react to oral nickel challenge¹⁹⁻²¹. After oral challenge IL-5 significantly increased in SNAS subjects, whereas no changes were found in DAC patients and in controls (Fig. 2)²⁰.

In our previous study²⁰ we found, after oral exposure, statistically significantly increased serum level of IL-5 while the modifications of IL-2, IL-4, IL-13 and INF- γ were not statistically significant. It was seen, 24 hours after Ni administration, a decrease of blood "virgin" CD4-CD45RO- lymphocytes in non-allergic subjects. This modification may be referred to transformation of these cells in CD4-CD45RO+ "memory" lymphocytes.

Fig. 1. Effect of nickel on NK cell activity. The effect of 100 μ g/ml nickel-sulphate was measured in triplicate on the NK cell activity of 24 patients with SNAS and 24 controls after 2 h of incubation. The effectors to target (K562) cell ratios are indicated.

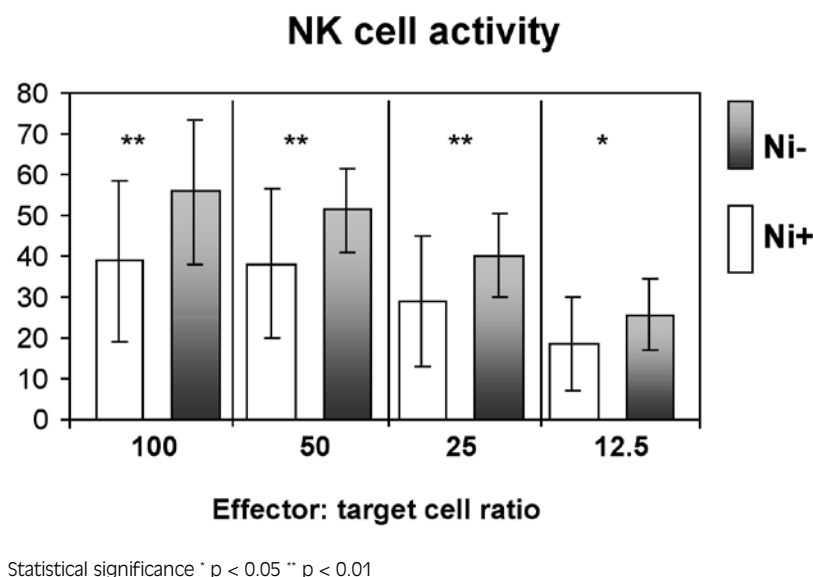
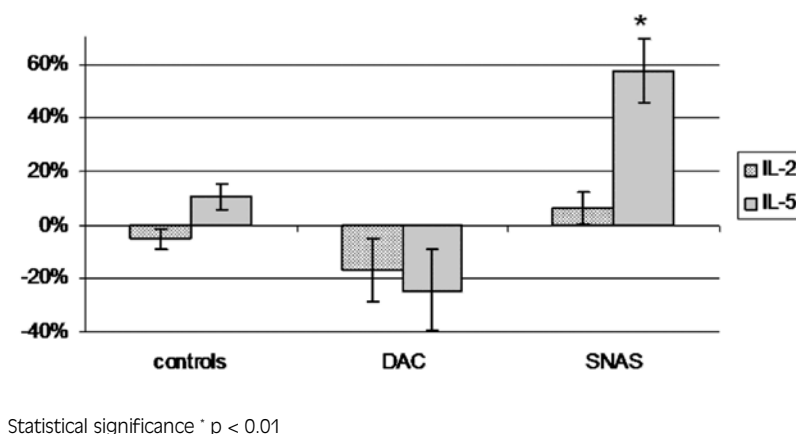


Fig. 2. IL-5% changes 24 h after oral nickel challenge in control subjects in patients with Ni-DAC and Systemic Nickel Allergy Syndrome. Significant changes were found in SNAS subjects.



However, these inflammatory alterations cannot be interpreted as a specific nickel reaction, because any recurrent contact with any antigen can induce an increase in CD45RO+ "memory" cells.

It has also been observed an increase of CD8+ lymphocytes 24 hours after Ni ingestion in non-allergic subjects. Such data is difficult to explain since it is known that Ni binds to class II proteins of the major histocompatibility complex presenting cells to CD4+

lymphocytes and seems not to have direct effects on CD8+ lymphocytes.

"Non-responder" and "responder" Ni-sensitized women showed higher values of CD19+ and CD5-CD19+ lymphocytes; this immune modification may be referred to an activation of the immune system without increase of serum IgE, which are produced by the B lymphocytes.

Szepletowski et al.²² and Ulfgren et al.²³ studied cutaneous biopsies drawn in the site of patch test. In the first work has been evaluated, through mRNA extraction, cytokines production in the site of patch test and in an other site of the same patient. The results documented an increased, statistically significant, expression of mRNA for INF- γ , IL-2, IL-4, IL-10 after nickel exposure. The limit of this study was the limited number of patients.

In the second work Ulfgren et al. evaluated cytokines production through an immunohistochemical analysis of cutaneous biopsies drawn in the site of patch test and in sites of application of irritants. Cytokines production was the same in both groups: increase of IL-2 and IL-4; only INF- γ production was greater in biopsies drawn in sites of application of irritants.

Borg et al.²⁴ described the release of cytokine from NiSO₄-stimulated PBMC from nickel allergic patients. Nickel-stimulation did not give rise to significantly differences in the cytokine ratios for IFN- γ and

TNF- α ; but induced a relevant increase of IL-4 and IL-5. Such data have been confirmed by the study of Budinger et al.²⁵ in NiSO₄-stimulated PBMC and of Jakobson et al.²⁶ that observed also a higher production of IL-4, IL-5, IL-13 and INF- γ from NiSO₄-stimulated PBMC of nickel allergic patients.

This finding showed that nickel stimulation of the PBMC obtained from nickel-allergic individuals induces secretion of both Th1 and Th2-type cytokines. This is in contrast to the results of several similarly designed studies showing that a Th1 cytokine profile develops in such individuals^{27,28}.

Further studies are needed to elucidate the precise involvement of these cytokines in the disease mechanisms of nickel-induced Systemic Contact Dermatitis. In conclusion, a definite dose-response reaction pattern to oral nickel exposure was observed among nickel-sensitive individuals. Nickel-sensitive individuals who had cutaneous reactions to the oral challenge with nickel showed significant increase of CD45RO+ in the gastrointestinal mucosa, suggesting maturation of T lymphocytes from virgin into memory cells. This immune reaction also involves CD8+ lymphocytes. IL-5 (able to activate eosinophils) seems to be a cytokine also important in the Systemic Nickel Allergy Syndrome, indicating an activation of Th2 lymphocytes in the peripheral blood.

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