Contact sensitivity to metals (chromium, cobalt and nickel) in childhood *

Alergia de contato aos metais (cromo, cobalto e níquel) na infância

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Abstract: Metals, especially nickel, are the most common contact allergens in children. Recent data has shown increased incidence of allergy in industrialized countries. Sensitization can occur at any age, even in neonates. Costume jewelry, particularly earrings, is linked to increased sensitization to nickel. Sensitization to cobalt often occurs by the use of costume jewelry. The most common source of sensitization to chromium is leather. Due to the absence of a specific therapy, the main treatment is to identify and avoid the responsible allergens. This article presents an updated view on the epidemiological and clinical aspects of contact allergy to metals, focusing on prevention strategies and risk factors, and warns about possible and new sources of contact. Keywords: Child; Chromium; Cobalt; Dermatitis, allergic contact; Dermatitis, contact; Nickel

Resumo: Os metais, especialmente o níquel, são os sensibilizantes de contato mais comuns em crianças. Dados recentes revelam aumento na incidência da alergia deste em países industrializados. A sensibilização pode ocorrer em qualquer idade, mesmo em recém-nascidos. Bijuterias, especialmente brincos nas orelhas, são ligadas ao aumento da sensibilização ao níquel. A sensibilização ao cobalto geralmente ocorre pelo uso de bijuterias. A fonte mais comum de sensibilização ao cromo é o couro. Devido à ausência de terapia específica, o principal tratamento consiste em identificar e evitar os alérgenos responsáveis. Este artigo pretende apresentar uma visão atualizada sobre os aspectos epidemiológicos e clínicos da alergia de contato aos metais, focando estratégias de prevenção e fatores de risco, além de alertar sobre as possíveis e novas fontes de contato. Palavras-chave: Cobalto; Criança; Cromo; Dermatite alérgica de contato; Dermatite de contato; Níquel

INTRODUCTION

Contact allergy is caused by environmental exposure to external agents that in contact with the skin trigger an inflammatory reaction. The precise incidence and prevalence of contact sensitization are not well known in the pediatric population. It is estimated that 28% of adults have contact allergy. 1 Allergic contact dermatitis (ACD) is often under-diagnosed, and this can be attributed to the infrequent performance of the patch test in children and to the fact that, in practice, the symptoms of the disease are misdiagnosed as other eczematous eruptions, such as atopic dermatitis and irritant skin reactions. It usually affects the lives of patients negatively. When acquired in childhood, it brings lifelong consequences, including in terms of occupational opportunities. The identification of the allergen through patch testing has improved patients’ quality of life. 2

Sensitization can occur at any age, even in newborns, which shows that the immune system in children presents an appropriate response to contact allergens from an early age, though they are possibly less often sensitized than adults. 3 4 Metals are the most common contact sensitizers in children and adults, especially nickel. 5-18 Fashion and lifestyle play an important role in the development of this sensitization. Nickel is a ubiquitous metal used in a wide variety of products, from military, health care, household and architecture utensils to the aerospace and transportation industries. It was considered the contact allergen of 2008 in the journal...
Dermatitis. Recent data have shown an increase in the rate of nickel allergy in industrialized countries, including high levels of sensitivity in children.

PATHOPHYSIOLOGY

ACD corresponds to type IV immune response, with an induction phase (afferent pathway) and an elicitation phase (efferent pathway), involving a complex series of events.

In the afferent pathway, a chemical substance of low molecular weight (hapten or incomplete antigen) enters the stratum corneum and reacts with components of the immune system. It covalently bonds to skin proteins resulting in a complete antigen. This hapten-protein conjugate binds to Langerhans cell (LC) membrane glycoproteins. Hapten needs to remain in the skin 18 to 24 hours for sensitization to occur. The LC-bound antigen migrates to the regional lymph node where it comes into contact with T cells. A group of T cells differentiates into memory cells and another differentiates into effector cells that circulate throughout the body, leading to the spread of contact sensitivity. The minimum time for the afferent pathway to be completed is four to five days.

The efferent pathway occurs when a previously sensitized individual comes into contact with the antigen for a second time. Initially the process is the same as that for a nonsensitized individual. Antigen recognition is done by antigen-specific memory T cells, which migrate to where the antigen entered the skin and, within 24 to 48 hours, the inflammatory reaction develops. Although reversal of contact sensitivity is uncommon, the magnitude of the allergic reaction may vary over time in each individual. This observation suggests that sensitization and expression of ACD are highly regulated by multiple events, ranging from nonspecific events such as induction of T cell anergy, to specific events such as induction of T cells with regulatory function. CD4⁺ T cells can be divided into two categories, Th1 and Th2, which are identified based on the cytokines they secrete. More recently, a similar heterogeneity between CD8⁺ cytotoxic T cells (cT) has also been recognized with the identification of the Tc1 and Tc2 subpopulation. Until recently it was believed that the most important effector cells for the development of ACD were CD4⁺ T cells. However, there is growing evidence that in many instances CD8⁺ may be the predominant effector cells. The greatest effect in the pathogenesis of ACD would be mediated by CD8⁺ T cells, whereas Th1 and Th17 cells would be more involved in the amplification of allergic reactions. Once activated, T cells release cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF)α and interleukin (IL)-17; keratinocytes release large amounts of cytokines and chemokines. In addition, IFN-γ and IL-17 synergistically regulate the expression of keratinocytes. Animal studies have been conducted and may lead to new therapeutic strategies.

EPIDEMIOLOGY

Risk factors for the development of ACD include the inherent sensitizing potential of the allergen, its concentration (dose per body surface area), high frequency and long exposure, occlusion, the presence of factors that increase the penetration of the allergen, and functional skin barrier changes. Sensitization has been recognized to influence the development of dermatitis caused by nickel. Apparently, the chloride radical CL present in sweat promotes the dissolution of nickel, allowing the action of its salts and justifying the aggravation of dermatitis in the summer.

Contact dermatitis occurs less frequently in the first months of life and its prevalence increases over the years. The most recent hypothesis is that its incidence gradually increases from birth until 14 years of age, remaining stable thereafter, with variations for some allergens depending on exposure pattern. Until recently contact dermatitis was considered uncommon in children, due to presumed paucity of exposure to allergens and lower susceptibility of the immune system. However, recent studies show that ACD in children is a significant clinical problem. Studies have found different rates of reactivity in children, depending on selection criteria, such as age, sex and type of population tested.

Weston et al conducted a review of U.S. and European studies involving children from birth to 14 years of age. They concluded that ACD represents up to 20% of all dermatites in childhood. Mortz and Andersen, in an evaluation of 17 studies of children under 16 years of age with dermatitis (sample size from 53 to 1,023 patients per study), observed a frequency of patch test positivity in 14.5 to 70.3% of cases, with relevance of 56.4 to 93.3%. A selection bias may explain the high reaction rates in some studies. Moreover, methodological variations complicate inter-study comparisons of results.

Infants and newborns can become sensitized. In 1931, Strauss used crude extract of Rhus toxicodendron radicans (poison ivy) to experimentally sensitize 38 of 45 newborns between one and four days of life; this experience was later reproduced by Epstein in 1961. Fisher reported the case of a one-week-old infant who developed an eczematous lesion on the wrist, where a vinyl ID wristband had been placed. The band was placed on the opposite forearm and the eruption was reproduced in two days. Patch testing with epoxy resin was strongly positive.

Some studies show predominance in women,
especially in relation to nickel and cobalt, \(^9,29-33\) while others show the same sensitization level for both sexes. \(^30\) Mortz \textit{et al} found a significant difference for nickel in an unselected population of adolescent students (13.7% women vs. 2.5% men), and no difference was found for the other 20 allergens with positive reaction. \(^30\) The findings indicate that sex differences are secondary to exposure and inherent to sex. \(2,20,34\)

Studies have sought racial differences between whites, blacks and Asians, with mixed results. Some differences in relation to the biophysical properties of the skin are observed, but definitive conclusions are difficult due to intra- and inter-study variability. \(^35\) The prevalence of ACD is similar in black and white skin. Some authors have studied physical and chemical differences and susceptibility to allergens, and have suggested that black skin is more resistant than white skin. Many of these claims are difficult to interpret due to socioeconomic differences and environmental factors. \(^20\)

The association of atopic dermatitis (AD) and ACD remains controversial. Some authors believe that AD does not affect sensitization to different allergens, although a higher number of irritant or false-positive reactions when patch tested is often observed in cases of active disease or those with severe skin xerosis. \(26,36,37\) Studies have shown both a slightly decreased risk or similar or higher prevalence of ACD among atopic patients. \(39,58-41\) In most studies, a significant difference between atopy and non-reactive and reactive metals is not observed.

Silverberg \textit{et al} observed a significant family history in children with allergy to nickel, suggesting that this factor may be a positive predictor for ACD to nickel. Therefore, a positive family history of reactivity to nickel would allow parents and patients to avoid contact from early childhood. \(^42\)

Some studies have shown that patients who had oral contact with nickel-releasing braces (dental braces) at an early age, and prior to the use of earrings, showed a lower frequency of nickel sensitivity when compared to patients who did not wear braces. This suggests an induction of immune tolerance by mucosal exposure to nickel. \(^42\)

The prevalence of nickel allergy among children in the general population is 0.9 to 14%; chromium 0.2 to 7.6%, and cobalt 0.5 to 5.7%, varying by age, sex and the population studied. \(^7\) Patients allergic to metals are often allergic to more than one metal. It has been suggested that this is not due to cross-reaction, but instead to co-sensitization, that is, the contamination of various metals in commercially available objects. \(35,43-46\)

**SOURCES OF CONTACT**

Nickel, a silver-colored metal, was first identified in 1751 by the Swedish mineralogist Barol Axel Fredrik Cronstedt. \(^47\) In the 19\(^{th}\) century, after the discovery of the method for its extraction, it was quickly used in large quantities due to its attractive qualities such as resistance to corrosion, durability and the fact that it binds easily to many other metals. \(^19\)

The first report of ACD caused by nickel appeared late in 1880. The disease was described by Blashcko \(^**\) as “galvanizing eczema,” a skin disease seen in the hands and forearms of miners and workers in nickel industries. \(^24\) It was initially considered an occupational dermatosis, but it began to affect the general population in 1950 when nickel was incorporated into products such as zippers, suspenders and jewelry. The prevalence and etiology of sensitivity to nickel reflect behavior and fashion trends. In recent decades costume jewelry, especially earrings, worn at an early age and, more recently, the increasing number of body piercings, have been consistently linked to increased sensitization to nickel. Gold, whether yellow or white, may contain nickel in enough quantity to cause sensitization when present in earrings. \(39,48\)

Several European studies have reinforced the role of detergents in triggering dermatitis, particularly hand eczema in individuals sensitized to metals, as they may contain nickel, chromium and cobalt. \(25\) Nickel may be present as a contaminant in cosmetics. Because the skin of the face, especially that of the eyelids, is very sensitive, metals present in cosmetics may cause dermatitis in sensitized individuals. The use of mobile devices, more and more common, including by children, is another possible source of contact that is often neglected.

Biomedical devices rarely produce localized or systemic reactions. Stainless steel, vitallium and titanium are alloys used in orthopedic prostheses. These metals are resistant to corrosion by physiological fluids and can be left in the body indefinitely. Vitallium alloy is composed of cobalt, chromium and molybdenum. Stainless steel is composed of iron, chromium, nickel, molybdenum and sometimes of small amounts of other metals. During the production of stainless steel, there is the formation of a crystal network involving metals, making them adhere firmly to one another and reducing the likelihood of sensitization. \(^49\) However, sufficient quantities of the metal can escape and cause dermatitis in sensitized individuals when there is continuous contact with the skin associated with perspiration, or when used in implants. \(25\) Consultation requests from orthopedic surgeons and orthodontists regarding the safe use of metal equipment in individuals sensitized to nickel are not rare. In cases of allergy to nickel, cobalt or chromium, titanium prosthesis may be preferred. The usefulness of the patch contact test preoperatively is unclear. It is recommended that patients with a history of allergy to
the metal perform the test and avoid implants containing the metal to which they are sensitized. Only long-term prospective studies can determine the need for this precaution. There are doubts about the role of metal allergy in endovascular stent restenosis and reports that patients sensitive to nickel present dermatitis as a result of nickel release by peripheral venous catheter.

The level of nickel in food is determined by components of the soil where the food is grown, by fungicides and by the equipment used in harvesting. This level may vary considerably between regions. Nickel is found in natural food like vegetables, nuts, cereals, potatoes, cocoa and fish. It is also found in water and cooking utensils. It can be released from stainless steel when the pH in boiling water is acid.

Complementary and alternative medicine such as homeopathic remedies and multivitamin complexes have been considered as additional sources of nickel with risk of systemic contact dermatitis in sensitized individuals.

Chromium was discovered in 1797 by the French chemist Louis Nicolas Vauquelin. It is the fourth most commonly found substance in the earth’s crust. In contrast to other metals, chromium allergy has been reported to be stable or declining. It is mainly used in metallurgy to increase corrosion resistance and give a glossy finish; in alloys such as stainless steel; in plating processes (depositing a protective layer of chrome on objects); in dyes and paints, in leather tanning and wood preservation. Detergents and cosmetics may also contain chromium. Historically, the most important cause of allergy to chromium has been occupational exposure to cement. In children, the most common source is leather, and chromium sensitivity is the largest responsible for shoe contact dermatitis.

Cobalt is a hard, silver-gray metal usually found associated with nickel. It was discovered by George Brandt, on an unknown date that varies, according to different sources, between 1730 and 1737. It is used in the production of metal alloys and pigments (cobalt blue and cobalt green). Sensitization to cobalt occurs mainly because of its presence in objects that also contain chromium and nickel and is often associated with allergies to other metals. In many cases sensitization is due to the use of costume jewelry. Detergents and cosmetics may also contain cobalt.

Allergic reactions produced by metal salts used in tattooing are not uncommon. The green pigment contains chromium, cobalt blue and black nickel. Chromium particles can remain dormant in the tattoo for 20 years or more, and suddenly produce allergic dermatitis.

**CLINICAL MANIFESTATIONS**

The classic clinical presentation of ACD is pruriginous eczematous dermatitis. In most cases it is difficult to differentiate the lesions clinically and histopathologically from atopic or irritant dermatitis. Clinical findings that increase diagnostic suspicion include recent onset, progression or deterioration of preexisting dermatitis, involvement of specific sites (face, eyelids, hands, and others), recalcitrant dermatitis and clinical presentation of dyshidrosis. Usually, the location of the eruption coincides with the site that was exposed to the allergen.

The classical symptom of dermatitis caused by nickel is a rash in the earlobes, periumbilical region or wrists resulting from contact with costume jewelry, buttons and zipper. Nickel is a frequent component of a large quantity of products, including keys, coins, scissors, pliers, costume jewelry, door handles, belt buckles and buttons. Prominent pruritic periumbilical papules (PPPP) have been suggested as a sign of ACD by nickel.

Thirty to forty percent of people sensitive to nickel develop hand eczema, which appears to be aggravated when there is concomitant allergic to cobalt. The finding of dyshidrosiform dermatitis with vesicular lesions and recurrent, pruritic lesions in the palms and fingertips is frequent.

Small amounts of nickel can be transported by fingers to areas beyond the contact. Up to 50% of children with ACD induced by nickel may present with distant or widespread eruptions, a reaction called “id”. It is usually symmetrical and related to activity in the primary site of contact. They typically appear as erythematous papules on the arms and thighs and may also involve the face and neck. They are often more refractory than the reactions that occur in the areas of real contact with the allergen, persisting for weeks to months. It is possible that some areas with little perspiration do not develop dermatitis when in contact with nickel in individuals who are sensitive to this metal.

Systemic contact dermatitis may occur after oral ingestion of nickel by sensitized individuals. This eruption has a latency period of a few hours to a few days after exposure and is often underdiagnosed. Skin reactions include aggravation of pre-existing lesions, vesicular hand eczema, flexural dermatitis, maculopapular exanthema, urticarial reactions and vasculitis-like lesions. The baboon syndrome, described by Andersen et al in 1984, is a typical presentation of systemic contact dermatitis and shows a classical distribution pattern of maculopapular erythematous lesions, pruritic and confluent, located in the gluteal and flexural regions. The red color of the buttocks, similar to baboons, explains the name of the syndrome.
Metals can cause noneczematous dermatitis. Contact with cobalt can trigger purpuric lesions, while contact with nickel and copper triggers lichenoid lesions. They can also lead to the appearance of pustules due to follicular obstruction. Some metals are able to induce a granulomatous reaction when introduced into the skin of sensitized individuals. Chromium and cobalt in tattooing can produce sarcoid granula.

Diagnosis

The diagnosis is based on clinical history, with emphasis on previous exposure. A delay in the onset of the reaction of 24 to 48 hours after exposure to the allergen may make it difficult to establish a causal relationship, since children and parents seek immediate associations. A detailed history of events during the week preceding the onset of symptoms should be obtained.

The most useful and reliable method for the diagnosis of ACD is the patch test, whose etiopathogenic mechanism is the same as that of ACD. When an individual is patch-tested, there is an attempt to induce the efferent pathway of type IV immune response. It has been used with children since 1930, but without standardization, as the specifications for the test in this age group are controversial. Several authors suggest lower concentrations than those used in adults due to the risk of irritant reactions and false-positive results. Others believe that the risk of such reactions would be nonexistent after seven to eight years old. Fisher proposed half of the concentration for nickel sulfate and potassium dichromate. Hjorth recommended that the concentrations be adjusted by age. Roul et al opined that future studies should be conducted with lower concentrations of metals for better resolution. Jacob et al reasoned that children may show physiological differences in relation to skin barrier and immune mechanism, leading to the need for research to standardize the patch test in this age group. However, the general view today is that children can be tested with allergens standardized by the International Contact Dermatitis Research Group (ICDRG). False-positive reactions are usually follicular and quickly fade after the removal of the test, unlike specific reactions, which remain for several days. The biggest problem of the test in children continues to be the small body surface area available on the dorsum. The application of tests with a reduced number of allergens overcomes this limitation.

The use of the patch test in children has increased in recent years and is considered a safe procedure. Sensitivity caused by the application of the test has not yet been reported. Scarring is very rare; there is only one report in the literature of appearance of keloid after the test in a ten-year-old boy tested for the second time for potassium dichromate, with an irritant reaction and progression to keloid after four months.

The Brazilian Group for the Study of Contact Dermatitis (BGSCD) standardizes the same terminology as that of ICDRG for the patch test: $- =$ no skin changes, $+$ = weak reaction (nonvesicular), $++ =$ strong reaction (vesicular); $+++$ = extreme reaction (bullous or ulcerated); $?+$ = questionable reaction (erythema without infiltration) and $IR =$ irritant reaction.

Intradermal testing with metal salts should be considered an investigative procedure because there is no agreement on its standardization, its significance and advantages or disadvantages.

Due to the fact that the patch test has some limitations (interobserver variability, restrictions on the patient’s routine, influence in the result by ultraviolet irradiation and the use of topical or systemic corticosteroids), an in vitro test is desirable. Several of them have been cited in the literature, but none with sufficient evidence for diagnostic use, mainly due to low sensitivity and/or specificity. The lymphocyte proliferation test (LPT) was introduced in 1970 and is still used, especially in experiments. In this test, the patient’s blood lymphocytes are put in contact with nickel. In patients sensitized to this metal, their memory lymphocytes are activated and incorporate radiolabeled thymidine, being thus possible to measure cell proliferation. The drawback is the need for a complex infrastructure of personnel and equipment, which makes the procedure costly. Sanches et al found 84.21% sensitivity and 100% specificity in the LPT.

TREATMENT

Due to the absence of a specific therapy and the permanence of sensitization, the main treatment is to avoid allergens. Untreated, lesions can persist 14 to 28 days despite the interruption of contact with the allergen.

Antihistamines or immunosuppressive therapy can be used to treat the symptoms. Oral and topical corticosteroids have a supporting role and should be used for short periods. We should bear in mind that the use of topical corticosteroids leads to the risk of atrophy, telangiectasias, tachyphylaxis and systemic absorption, especially in areas of high sensitivity such as face and flexures. Topical immunomodulators such as pimecrolimus and tacrolimus provide a steroid-sparing option.

Once the allergen is identified, the patient should be adequately educated about preventive measures. Traditionally, the patient who is allergic to nickel is advised to avoid any exposure to costume jewelry and other metal products. However, many children...
and adolescents find it difficult to follow these guidelines due to extensive exposure to nickel. Although it is common to cover pant buttons with enamel or adhesive tape, this practice is generally unsatisfactory due to sweat. In one study, 90 buttons on jeans pants and 47 belt buckles were tested with a kit for detecting nickel. Only nine (10%) of the total jeans pants tested showed the presence of nickel, while 25 (53%) of the belt buckles were positive. The role of sweat and daily use were not analyzed in this study. It is possible that buttons that tested negative for nickel release the metal over time.

An easy-to-use kit for detection of nickel in metal objects is commercially available under the name Ni Test® and can be purchased via the Internet. The test has two reagents (dimethylglyoxime and ammonium hydroxide) and consists in applying a drop of each solution to an applicator like a cotton stick swab, which is then rubbed on the object to be tested. The applicator will turn pink if the object contains a nickel concentration of at least 1:10,000. Family members should be advised to purchase the kit to help in the identification of nickel in clothing and personal belongings.

Some authors recommend a diet low in nickel for dermatitis induced by this metal, particularly in vesicular hand eczema unresponsive to traditional treatment or recurrent dermatitis for no apparent reason. They are usually uncontrolled studies, hindering the interpretation of the results. Jensen et al, in order to determine the threshold limit value for oral exposure to nickel that could trigger eruption in sensitized individuals, combined data published from January 1966 to November 2004. They concluded that only 1% of sensitized patients would present systemic contact dermatitis with daily exposure to 0.22 - 0.35 mg of nickel coming from water and food.

The ears should be pierced with stainless steel instruments and only surgical steel earrings should be worn until complete epithelialization of the opening, which occurs, on average, after three weeks. Nickel can penetrate rubber but not vinyl gloves. Therefore, vinyl gloves must be worn by sensitive individuals when they are in manual contact with nickel. Preference should also be given to aluminum, Teflon or enamel cookware.

An effective tool for primary and secondary prevention of allergy to metals is to limit the level of these metals in some products. Investigations have shown that induction of contact allergy to nickel depends on the quantity of this metal per area of skin, and on the fact that nickel could be released as a response to the corrosion caused by human sweat. Based on research, 0.5 μg/cm² of nickel released per week is suggested as a safe limit for exposure. In 1992 the Danish Minister of the Environment implemented a regulation of exposure to nickel limiting the release of this metal by objects that are in prolonged contact with the skin. The regulation seems to have had a positive effect, as demonstrated by Jensen et al in a population study of school-age children, in which there was a significant decrease in the frequency of sensitivity to nickel after its implementation. In 1994, a similar legislation was adopted in the EU banning the trade of products that release more than 0.5 g/cm² per week of nickel.

**CONCLUSION**

Metals are the most important contact allergens which affect children who are sensitized early through clothing and especially through the use of earrings. The regulation of the amount of nickel that can be released by objects that come into prolonged contact with the skin appears to be a solution that has benefited European countries. Pediatricians and dermatologists should be attentive to the several epidemiological and clinical aspects of ACD to metals, in addition to becoming familiar with possible new sources of contact. By doing so, they will be better equipped to act early to prevent the disease, thus avoiding sequelae in the adult life of these patients.

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