



Nickel contact dermatitis in children

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Abstract Nickel is the most commonly detected cutaneous allergen on patch testing in the United States for children. The ubiquitous nature of nickel as a hardening agent in metal products makes avoidance difficult. Allergy in childhood can be hard to recognize, especially when a strong idiopathic response is noted. Although the standard belt buckle and jewelry trigger still occur, newer sources include technology equipment, such as cases for mobile phones, computers, and tablet devices. This contribution reviews the various clinical appearances of nickel contact allergy in childhood, as well as strategies for treatment and avoidance.

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Introduction

Nickel is the most commonly detected cutaneous allergen on patch testing in the United States for children, with sensitization to nickel being reported to be as high as 26.8%.^{1,2} It is ubiquitous in the environment, being found in a large host of diverse products and materials, leading to almost constant levels of exposure.³ The incidence of nickel allergic contact dermatitis (Ni ACD), which appears to be increasing, is estimated to be 14% to 20% of women and 2% to 4% of men in the United States,⁴ and often is associated with skin piercing and adornment practices.⁴ That said, nickel sensitization is being recognized in nonpierced children and, despite the high prevalence of this disorder, recognizing the varied forms of allergic manifestations can be challenging for the practitioner.

Presentation

Ni ACD can be classified as local, ectopic, idiopathic, or systemic. Localized contact dermatitis appears in those areas that come into direct contact with metallic sources (eg, belt buckles) and usually presents acutely with a monomorphic grouping of erythematous to flesh colored papules at sites of metal contact, which can include pruritus, erythema, edema, and vesiculation. Less intense, or subacute, reactions can present with only mild edema, erythema, and minimal vesiculation. Chronic allergic contact dermatitis can present with xerosis, fissuring, lichenification, erythema, and excoriations, as is commonly seen on the earlobes or fingertips.⁵ Chronic rubbing of sites of Ni ACD may cause lichen simplex chronicus and/or lichenoid papules and plaques.

Idiopathic (“id” reaction) Ni ACD is typically a symmetric hypersensitivity reaction, also termed auto-eczematization, which characteristically involves the flexural extremities, eyelids, and sides of the neck and face, but can

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become generalized as well with time or with systemic nickel exposures. Skin-colored, erythematous, or lichenoid papules over the extensor skin surfaces or potentially across the full body surface area may be seen. Less common presentations of Ni ACD include erythema multiforme, urticaria, or prurigo.⁶

Of note, children with atopic dermatitis (AD) may experience an exacerbation of their atopic pruritus secondary to comorbid Ni ACD. The incidence of Ni ACD in atopic dermatitis, explored in a European cohort of adolescents and adults, was 28; 2% being the leading allergen in a patch test series.⁷ A series of Danish eighth graders with Ni ACD followed for 15 years revealed that Ni ACD was present in 11.8%, with an 80.8% clinical relevance.⁸ Patients with atopic dermatitis were more likely to have long-standing issues with Ni ACD and very few lost patch test positivity to nickel over time.⁹ The coexistence of AD often obfuscates the initial diagnosis of Ni ACD, especially in idiopathic- and systemic-type response with flexural involvement. Unlike AD, Ni ACD may at times be slower to clear with topical corticosteroids than atopic dermatitis; therefore, a therapeutic trial with a midpotency topical corticosteroid in children may obviate the presence of Ni ACD (personal observation, N.S.). The disease is usually more widespread in atopic patients; however, Ni ACD in one series was not associated with AD, while fragrance was associated.^{10,7}

Ectopic reactions have been observed in association with patient transfer of nickel residue via sweaty fingers that touch the primary area and then transfer the nickel to other parts of the body (eg, fingertips to eyelid after repeated handling a nickel lanyard, S.E.J. observation); this could then be the source of disease eccentric to the primary sites of exposure.¹¹ In addition, secondary contact points have also been reported (eg, flip phones where the metallic buttons touch the screen and then the nonmetallic screen transfers the nickel to the patient's face).

Systemic immune hypersensitivity (as part of the systemic nickel allergy syndrome) to nickel has been reported in association with ingested nickel and can result in the appearance of a type IV mediated hypersensitivity presenting as generalized dermatitis. This presentation is likely more common than previously realized.¹² Additionally, one group of authors has postulated that the systemic nickel allergy syndrome leaves patients more susceptible to recurrent infections, which may further aggravate disease appearance.¹³

Pathology

The histopathology of active lesions of nickel dermatitis reveals inflammation with intraepidermal intercellular edema, that is, spongiosis, as well as monocyte and histiocyte infiltration in the dermis, suggestive of a cell mediated immune response, typical of allergic contact dermatitis.¹⁴

Pathogenesis

The pathogenesis of nickel allergic dermatitis begins with the nickel antigen being taken up by the skin's dendritic cells, which in turn process and present the antigen to T cells (Th1 and Th17 cells).¹⁵ These sensitized T cells become clonal and traffic through the circulation to different skin areas. Such sensitized T cells mediate the release of cytokines from other cells all over the body.¹⁶ The release of these specific T-cell mediated cytokines, induces apoptosis of nickel-loaded keratinocytes through a perforin-dependent mechanism.¹⁷ In non-nickel-allergic individuals, the expansion of specialized T cells with regulatory function prevents an inflammatory response from occurring as well as reactive T cells from forming.¹⁸ In allergic individuals, there is a limited amount or absence of these T cells and, therefore, an inability to suppress an allergic immune response from occurring.⁵ There can be a genetic basis to Ni ACD caused by a T-cell receptor mutation in the CDR loops, which leaves patients prone to allergy to nickel.¹⁹ It is, therefore, not uncommon for patients to have a positive family history of nickel allergy. Nickel exposure appears to induce an effect on the innate immune system, engaging a toll-like receptor 4 (TLR-4) induced inflammatory response (inflammasome) in addition to the standard type IV mediated immunity, which is a specific human host cell response that is not present in mice.²⁰ In this setting, Ni triggers the inflammasome complex by heterodimerization of hTLR4/ hMD2, resulting in MYD-88-dependent activation of the IKK2/ NFKB and MKK3/6/p38 pathways mediated by mutation in hTLR4(19). CD 4+ T cells in patients with Ni ACD appear to produce IL-17, IL-22, and IFN- γ as effectors of cutaneous inflammation.²¹

Sources of exposure

Piercings and costume jewelry (watches), belt buckles and clothing fasteners (buttons, studs, and grommets) remain top sources for epicutaneous sensitization with dermatitis in the earlobes and infraumbilical areas predominating. One study found that 13% of 960 girls aged 8 to 15 with pierced ears were nickel allergic, whereas only 1% of those without pierced ears were.²² Interestingly, a Danish series found ear-piercing was associated with Ni ACD before EU legislation but not after.⁹

Sweat and friction of buttons and buckles against the skin can induce subclinical maceration, increasing the release of nickel and enhancing reactivity to metal, which comes in contact with the skin at the waistline. Other sources of nickel exposure can be the ball and chain metal dog tag necklaces, which are stylish for young children.²³ In warmer climates, metal tabs on seating in school chairs can be a source of nickel contact.²⁴ Exposure to nickel through release from technologic devices, such as metallic cell phone cases/

buttons, tablets, computers, and laptops, has recently been recognized as a potential source of allergen exposure.^{25–27} Other sources include dental amalgams and braces, and usage of metallic equipment, such as cosmetic applicators and eyelash formers (Table 1).^{28,29}

A significant source of nickel dermatitis in men is through occupational exposures; however, male piercings may also contribute to sensitization. Occupations with high risk of nickel sensitization include the metal industry, hairdressing, tailoring, and even hotel and restaurant work due to exposure to various cooking and cleaning instruments. Sweat and household detergents were shown to have the capacity to release nickel from stainless steel and white gold.^{30–32} Unfortunately, once a person is exposed to and sensitized to nickel dermatitis, the allergic reaction persists indefinitely.³³ Legislation from the European Union limiting nickel release from metal objects (including jewelry) has resulted in a reduction in nickel sensitization among European women, but street vendors and sewing materials from haberdashery shops seem to be ongoing exposure sources.^{34,35} Newer sources of nickel contact are becoming recognized worldwide, even in countries where EU legislation controls production.

Although sensitization to nickel occurs epicutaneously, the role of nickel food sustaining and provoking systemic nickel manifestations in exquisitely sensitized persons should not be underestimated.³⁶ A common location for systemic nickel dermatitis is the hands. Such hand dermatitis typically seen manifests as pompholyx, dermatitis accompanied by recurring itching, and the presence of vesicles in the palms and on the sides of the fingers, or regular hand dermatitis³⁷; however, generalized extensor surface dermatitis can be noted in children with nickel allergy, especially when systemic contact allergy is suspected.

Newer sources of nickel contact are becoming common worldwide even in countries where EU legislation controls production. These items include primarily metallic covers for cell phones, note pads, laptops, and other electronic devices (Table 1).

Differential diagnosis

Other allergens may be contributory to the clinical appearance and should be investigated via patch testing. Coexistence of Ni ACD with allergy to other metals, such as

Table 1 Site of Ni ACD in children and source of nickel

Site	Source
Eyelids	Eyelash former ¹ Eyeglass frames and optical wear ¹ Nail polish with metallic ball inside Eyeliner pencils
Face	Airborne exposure ¹ Oral exposure ¹
Lips/ Oral Mucosa	Dental amalgams ¹ Dental wire ⁸ Oral care items ⁸ Utensils ¹
Neck/ Ears (including nodules of the lobe)	Jewelry including earrings, ¹ dog tags, necklaces, body piercings ^{23,1}
Cheeks/ Malar	Cell phones and accessories ¹
Wrist	Watches ^{1,5} Bracelets ^{1,5} Wrist rests on laptops ¹ Wrist guards ¹
Hands	Utensils ^{10,7} Tools ^{10,7} Coin handling ¹ Toys ¹ Oral exposure ⁸
Dorsal thighs	Laptops, ¹⁷ tablets, ¹ notepads and pocket change, ¹⁹ sport pads ¹
Periumbilical or infraumbilical	Button flies, ^{1,5} belt buckles ^{1,5}
Hips	Grommets in pants ¹ Coins or cell phone in pocket ¹
Ventral thighs	Metal fittings on chairs ²⁴
Forearms, calves	Autoeczematization reaction ¹
Shoulders	Loops from overalls (personal observation) Sports pads ²⁴
Midline chest and shoulders	Metallic snaps (especially in infants) (personal observation)
Generalized	Food and dietary nickel sources including canned goods ¹

Table 2 Nickel-rich foods

Grains
Oatmeal
Oat ring cereal
Legumes
Beans (lima, pinto, white, etc.)
Chili
Refried beans
Lentils
Peas
Proteins
Clam chowder
Soybeans/ soy products
Shellfish
Processed meats with fillers
Canned meats/ fish
Fruits/Vegetable/Nuts
Asparagus
Canned vegetables
Peas
Chocolate
Seeds
Sunflower seeds
Drinks
Black tea
Pineapple juice
Prune juice
Tomato juice
Miscellaneous
Canned foods in general ^{49,50,51}

cobalt, is not uncommon and may be a result of epitope spreading.³⁸ In addition, impetigo, scabies, and inflammatory dermatoses, such as psoriasis, can produce persistent periumbilical plaques. Diagnosis of nickel allergy usually is determined by a good history and physical examination. Patch testing may suggest or confirm the etiologic agent in allergic contact dermatitis, but biopsies are of little diagnostic help.³⁹

In addition, scabies and inflammatory dermatoses, such as psoriasis, can produce persistent periumbilical plaques. Other diagnoses that mimic Ni ACD include mycosis fungoides, tinea corporis, atopic dermatitis, and fixed drug eruptions. Diagnosis of nickel allergy usually is determined by a good history and physical examination. Patch testing should be used to confirm the etiologic agent in allergic contact dermatitis. Biopsies may be of limited diagnostic help in chronic stages or when there are confounding diagnosis (ACD in an AD patient).^{1,5}

Treatment

Appropriate management of patients with Ni ACD typically involves treatment of symptoms, while avoidance measures are instituted.^{1,5} Education is the key component in

inducing patient compliance, especially with ubiquitous allergens such as nickel. These lifestyle adjustments include careful selection of clothing, jewelry, and belts that contain costume metal fittings, but in certain circumstances may also include changing what they eat, what they wear, where they work, and even what cooking utensils are used at home.

The patient should be taught to use the dimethylglyoxime ammonia spot test for nickel.⁴⁰ With this test, the patient can apply a drop of solution to a cotton-tipped applicator, rub the surface of the item in question, and if it contains nickel the swab will turn pink. The more nickel content the more robust the pink color will be. Equipping the patient with this useful tool will allow him or her to select safe alternatives in costume jewelry and clothing. Nickel is a common element in silver and gold plated jewelry, and it is often found in the underlying base metal of most plated jewelry.⁴¹ With gold jewelry, the lower karat gold alloys have greater percentages of “other metals” and should be avoided. For example, 10 karat gold is 41.67% pure gold and 58.33% “other metals,” whereas 18 karat gold is 75% pure gold and 25% “other metals.” Only 24 karat gold is 100% pure gold, and for this reason, it is the best type of gold for patients with nickel allergy to wear (unless they are gold allergic as well); however, most patients will be able to tolerate anything above 10 karat gold.⁴² Only yellow gold should be worn, as white gold is whitened, by adding to the yellow gold another alloy, which is usually nickel.

Silver jewelry should be limited to purer forms as well. For example, commercial silver is graded 925, which is 92.5% pure. Most patients will be able to tolerate this, but if not, then only the highest grade silver graded 980, which is 98% pure, should be worn.⁴³ With regard to clothing, nickel button flies can be removed, replaced with plastic ones, covered with fabric, or can be coated with clear nail polish every few days or after washing. Belt buckles should be tested for nickel, and the buckle should either be replaced with a non-nickel containing buckle (eg, brass), or painted with a non-metallic coating. Other clothing articles that may contain nickel and should be tested include buttons, zippers, bra hooks and under wire, all buttons and studs, and hair clips.⁴⁴ Perspiration, friction, pressure, and the amount of nickel that a particular alloy releases are directly proportional to the severity of the condition at clinical presentation; these variables also explain why the condition is almost uniformly worse in the summer.⁴⁵

Gloves should be used if a patient must routinely handle nickel-containing items.⁴⁶ Many items in the home are made of stainless steel, which usually contains a small amount of nickel. Usually, it will not aggravate most people with a nickel allergy, because its structure is such that the nickel is so firmly bonded in the alloy that it is unable to escape or to be leached out by perspiration or moisture.⁴⁵ That said, acidic foods have been known to increase leaching, so as a precautionary measure, food should preferably be cooked with aluminum utensils in enamel or glass pans that give a negative test for nickel.⁴⁷

In patients with systemic nickel dermatitis, avoidance of direct contact with nickel must be supplemented with avoidance of excess iron intake. Several studies have also reported that an iron-depleted state facilitates increased nickel absorption, and foods rich in iron (and low in nickel) are recommended. These iron-rich foods include beef, pork, lamb, liver and other organ meats, chicken, turkey, wild game, and fish.^{48,49,50} Similarly, ascorbic acid-rich foods, including strawberries, citrus fruits, and broccoli, are recommended because they may enhance iron but decrease nickel absorption.

Low nickel diets (diets with restriction of nickel to less than 100–150 µg/day) have been proven to be beneficial for some patients,⁴⁹ including those with chronic hand dermatitis, who were sensitized. Nickel-rich foods are listed in Table 2. Until recently, the guideline for patients with systemic nickel allergic dermatitis was to avoid all possible nickel-rich containing foods, without any consideration for the health consequences of a low nickel diet. Due to the difficulty in compliance with these diets, low points diets were developed to assist the patient in selecting high point foods to avoid. In 1993, the FDA proposed that an intake of 50 µg of nickel is a tolerable dose for hypersensitive individuals.^{48,50} The revised nickel plan also calls for avoidance of processed or restaurant foods due to the uncertain amounts of nickel. A recent contribution created a points system for nickel ingestion, recommending that children not have more than 10 and adults more than 15 points a day for nickel ingestion. The authors recommend avoidance of all chocolate, soy, beans, oatmeal, and granola and cooking only in nonstick cookware. They caution against cooking acidic foods in stainless steel cookware. They recommend vitamin C (500–1000 mg) intake with meals to reduce nickel absorption.⁵¹ Nickel-free diets have also been used recently in gastroenterology as an adjunctive agent for the eradication of *Helicobacter pylori* via antibiotic regimens.⁵¹

The importance of nickel in a person's diet is now being reconsidered, as nickel may participate in the absorption of important minerals, such as zinc, copper, and vitamin B12.^{48,52} In addition to its absorptive properties, nickel has also been found to play an important role in sperm physiology. In rat studies, nickel deprivation significantly reduced spermatozoa motility and density. The application of these results to human models has not yet been investigated.⁵¹ With this new appreciation of the potential role of nickel in a healthy diet and life, the goal of treatment has been modified so that nickel should not be completely avoided, but instead that its intake be restricted to a level that is both tolerable to the patient and does not cause a deficient state.

Avoidance of nickel can be a seemingly insurmountable task, and even with diligent avoidance not all patients can immunologically reset. There are many pharmaceutical therapies for nickel dermatitis, which are aimed both at ameliorating symptoms as well as preventing future occurrence. Symptomatic care with topical midpotency

corticosteroids and antihistamines can be used to temporarily relieve the pruritus that often accompanies nickel dermatitis, and established treatments for nickel dermatitis include UVB phototherapy and corticosteroids.

The efficacy of topical steroids in the treatment of nickel dermatitis has been well documented, and in a double-blind, placebo-cream controlled study, 0.05% fluticasone propionate (Cutivate cream) was effective in reducing nickel-induced contact allergy.⁵⁴ Often, however, patients are unresponsive to these treatment modalities, and, even in cases in which successful treatment is achieved, the associated potential risks and side effects associated with long-term corticosteroid use sometimes makes their use inappropriate and inadvisable. Long-term oral use and widespread topical use can result in cutaneous atrophy, hirsutism, folliculitis/acne, and systemic absorption.⁵⁵

Phototherapy is generally reserved for patients with refractory nickel dermatitis that is unresponsive to topical or oral corticosteroids. Ultraviolet light has intrinsic immunosuppressive properties, and several studies have shown that oral psoralen photochemotherapy (PUVA) and shortwave ultraviolet light (UVB) can be highly effective in the treatment of chronic nickel dermatitis. In an uncontrolled study, UVB had an excellent effect in 7 of 10 patients with allergic contact dermatitis of the hands.⁴⁰ The treatment duration was on average as long as 5 months, and maintenance therapy was usually required.⁵³ The same study showed that, although PUVA may be superior to broadband UVB for the treatment of chronic hand dermatitis, it was also more phototoxic and should only be used after a patient had failed treatment with UVB. The length of treatment necessary, as well as the need for maintenance therapy, brings with it the associated risks of phototoxicity.

In the past decade, however, the use of immunomodulatory and antiinflammatory agents have brought much new and needed hope in the treatment of nickel dermatitis. These agents work by targeting specific mediators or pathways of inflammation. The calcineurin inhibitors work by inhibiting the protein calcineurin, subsequently preventing the dephosphorylation of the nuclear factor of activated T cells (NF-AT), a transcription factor. As a result, the signal transduction pathways in T cells are blocked, and inflammatory cytokine production is inhibited.⁵⁶ Tacrolimus has been shown to help with the clinical manifestations of ACD. The most common side effects of topical tacrolimus use were burning and stinging at the site of the application. As opposed to topical steroid use, tacrolimus ointment is not associated with skin atrophy.⁵⁷ Pimecrolimus is effective as well at reducing Ni ACD.⁵⁶

Some pharmacotherapies that are currently under investigation include the use of NADH,⁵⁸ the reduced form of B-nicotinamide adenine dinucleotide, phosphodiesterase inhibitors⁵⁹ and mycophenolate mofetil,⁶⁰ all of which work in different ways to ameliorate the signs of allergic contact dermatoses. Additionally, in a recent study, the topical application of 100% tea tree oil (an emollient known

for its antimicrobial effects but largely only anecdotally for its antiinflammatory effects) was shown to have therapeutic benefit, as well in the treatment of nickel dermatitis; however, this therapy would be limited by the fact that tea tree oil is allergenic, as well.^{17,61} Oral nickel hyposensitization is under testing, but safety in childhood has not yet been established.⁶² These alternative and investigatory therapies may eventually become standard of care.

Conclusions

Pediatric Ni ACD is common and difficult to eliminate. The mainstay of therapy is avoidance, which is more effective when instituted early. Dietary restrictions and systemic immunosuppressive medications may be necessary in exquisitely sensitized individuals. As has been seen in Europe, manufacturing legislation is an important and needed to reduce the future burden of this disease. As importantly, control and oversight of overseas manufacturing needs to occur to ensure such legislation is enforced.

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