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Systemic Contact Dermatitis in Children: How an Avoidance Diet Can Make a Difference

Catalina Matiz, M.D., and Sharon E. Jacob, M.D.

Division of Dermatology, Rady Children's Hospital – UCSD, San Diego, California

Abstract: **Systemic contact dermatitis is an under-recognized skin reaction that occurs secondary to systemic (oral, intravenous, intramuscular, inhaled, or subcutaneous) exposure to a hapten in a previously sensitized individual. Medicaments are the most common cause of SCD in the adult population, but other chemicals like nickel, cobalt, balsam of Peru, and formaldehyde have been implicated as well. Few reports in children exist to date. Dietary restriction has shown to be of some benefit in managing some adult patients. We present a case series of 8 pediatric patients diagnosed with SCD from the contact dermatology clinic, who showed marked improvement of their dermatitis after adequate dietary avoidance. We review common presentations of chemicals causing SCD in children and potential dietary modifications.**

In U.S.-based reports over the last year, allergic contact dermatitis (ACD) was shown to be as equally prevalent in children as it is in adults (1,2). Systemic contact dermatitis (SCD), defined as a skin reaction in previously sensitized individuals after systemic exposure to the allergen, which recently gained significance in adult populations, has also begun to be reported in the pediatric population with a handful of cases and series reported from Europe (3–5). The actual prevalence rates of SCD in both adult and pediatric populations are unknown, as there are no epidemiologic studies on the subject matter. One of the more extensively studied allergens, nickel, it was shown in a meta-analysis of 17 oral nickel exposure studies that 1% of nickel-sensitive patients demonstrate systemic reactions to dietary doses of nickel. We present the first U.S.-based case series of eight pediatric patients diagnosed with SCD who cleared their dermatitis following adherence to dietary restriction and topical avoidance.

METHODS

Eight symptomatic children (four girls and four boys) aged from 13 months to 16 years were referred for patch testing for recalcitrant or deteriorating atopic dermatitis and localized recalcitrant dermatitis. Patch testing was performed with individually customized allergen exposure-targeted batteries using standard (Chemotechnique Diagnostics, Vellinge, Sweden) application to IQ chambers™ (Chemotechnique Diagnostics), in addition to the patient's own personal care products and medicaments, with the exception of patients 6 , 7 and 8 who were solely tested with the TRUE test (Allerderm, Phoenix, AZ). Patch tests were then taped (with Hypefix™, BSN

Address correspondence to Sharon E. Jacob, M.D., Division of Dermatology, USCD – Rady Children's Hospital, 8010 Frost Street, Suite 602, San Diego, CA 92123, or e-mail: sjacob@contactderm.net.

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Medical GmbH, Hamburg, Germany) to clinically normal skin on the back for 48 hours and read at 48 and 96 hours. Subjects 6 years of age or less were read at 48 and 72 hours. Clinical relevance was assigned by the patch-testing physician as previously described (1).

RESULTS

The patients were confirmed to have ACD by association of a clinically relevant allergen with a positive patch-test reaction. Three patients demonstrated allergy to nickel, three to balsam of Peru (BOP), one to formaldehyde, and one to cinnamic aldehyde and propolis (Table 1). All eight patients demonstrated mild to moderate improvement of their dermatitis by topical/contact avoidance of their clinically relevant allergen. Follow-up visits with the patients and families demonstrated compliance with avoidance and frustration. Because some improvement was noted, we explored trials of systemic or dietary avoidance. This notably resulted in significant improvement in our patients. The majority of the patients had a significant clinical response with an avoidance diet within the first 6 weeks, and those who followed the diet for a longer duration had sustained improvement.

DISCUSSION

Systemic contact dermatitis was first described in 1895 by Jadassohn (6,7) as a skin reaction in previously sensitized individuals after systemic exposure (oral, intravenous, inhaled, subcutaneous, intra-articular, intramuscular, or transepidermal) to mercury (8). Different names have been coined for this skin reaction since its first description, including: systemically induced ACD (9), systemic allergic dermatitis (10), baboon syndrome (11), symmetrical drug-related intertriginous and flexural exanthema (when medication-related) (12), hematogenous contact eczema, mercury exanthem (5), and contact type dermatitis medicamentosa (13). Systemic contact dermatitis has also been described as flare-up reactions at previous sites of patch testing or initial sites of affliction in the adult populations (14).

Certain allergens are more likely to cause SCD than others and may have several presentations that could be clues for diagnosis, even though presentations can vary even for the same allergen. For example, many patients with nickel SCD allergy present with vesicular hand eczema (10). Flare ups of previous sites of exposure, as well as perioral and eyelid dermatitis, after ingestion of BOP or related allergens (cinnamic aldehyde, Compositae), are common presentations for BOP/fragrance SCD (10). Patients with mercury derivatives, nickel and medicament-associated SCD have been reported to present with flexural and gluteal erythematous plaques, also known as baboon syndrome (15).

Metals

The metals (nickel, cobalt, and chromium) are often described as commonly causing SCD, especially in cases of vesicular hand eczema (16). Nickel was found to be the most common allergen associated with food-associated ACD in 48.7% of 122 adult patients reviewed by the NACDG (17). According to one meta-analysis, SCD from oral exposure to nickel occurs in a dose-dependent fashion, and about 1% of exquisitely sensitized individuals can react to just 0.22 to 0.35 mg of daily nickel intake from foods or tap water (18).

In the cases covered in our series, we identified different nickel presentations of SCD in children, including vesicular hand eczema, localized eczematous reaction, as well as generalized eczematous exanthems. Our patients were prescribed low-nickel diets with significant clinical improvement noted as early as 6 weeks and increased and sustained responses after 12 weeks on the diet. The high-nickel-containing foods to be avoided in patients with nickel SCD are summarized in Table 2. In addition, limiting the ingestion of complementary and alternative medicaments with high nickel levels is recommended (19,20). Dietary restriction of nickel in an adult study showed that almost 50% of the patients improved their dermatitis following a low-nickel diet for at least 4 weeks (16).

Systemic contact dermatitis to cobalt, a common co-sensitizer with nickel, may also present clinically with vesicular hand eczema. A "point-based" low-cobalt diet proposed by Stuckert et al (21) was developed to help cobalt-sensitive patients limit consumption of cobalt to less than 12 μg per day, while improving compliance, because it permits consumption of certain cobalt-containing foods in moderation.

Botanicals

Balsam of Peru is a natural extract from the *Myroxylon pereirae* tree and is known to contain more than 400 different components. Fragrances and flavorings, specially those present in BOP, are known to be common instigators of SCD in adults (22,23). Systemic contact dermatitis to BOP can have variable presentations from dermatitis localized to the hands and face to generalized reactions (24). Several studies in adults with SCD to fragrances and BOP have shown that an avoidance diet may benefit about 50% of affected patients (23,25,26). Three of our pediatric cases following dietary avoidance of BOP had significant and sustained clinical

TABLE 1. *Cases of SCD (in Graphic Folder)*

Case	Age	Gender	History of AD	Location	Presentation	Allergen	Contactant	Avoidance	Diet
1	13 yrs	F	Yes	Thighs and trunk	Bilateral LE eczematoid plaques [began after started shaving]; nummular plaques scattered thighs, trunk	Nickel	Razor + DMG test	Leg dermatitis improved and nummular eczema slight flare in 9 wks.	Low-nickel diet—cleared at 3 mos f/u
2	13 mos	F	No	Oral labia, face and generalized	"Connubial contact" swollen oral labia, bilateral facial and fine eczematoid plaques on arms	BOP	Mother's perfumes; Flared with vanilla teething biscuits	Improved 80% in 10 wks.	BOP diet—cleared
3	3 yrs	M	Yes	Perioral	Perioral dermatitis and worsening of atopic dermatitis	BOP	PHP; Flared with vanilla and artificial orange lollipops	BOP/fragrances removed from PHP—50% improvement at 8 wks.	BOP diet – 85% improvement atopic areas mild, but remained
4	6 yrs	F	Yes	Perioral	Mild eczema and perioral dermatitis	Cinnamic aldehyde and propolis	ChapIce gentle lips cherry; Flared with gummy multi-vitamins	Cessation of all chap sticks/balms containing fragrances and beeswax; 70% improvement—mild swelling and lip eczema remained at 8 wks.	Removal of multivitamins —cleared
5	11 yrs	M	Yes	Eyelid, generalized	Generalized erythema and scale, eyelid dermatitis	Formaldehyde and aspartame	PHP	Formaldehyde and formaldehyde releasers removed from PHP—65% clearance in 8 wks.	Cessation of aspartame (montelukast and diet soda)—cleared
6	13 yrs	M	Yes	Periorbital, neck, axilla, trunk, arms, legs	For 1.5 yrs worsening of eczema and started presenting periorbital and neck dermatitis	BOP and fragrance mix I	PHP; Will flare with the consumption of spicy red sauces	Fragrance contact avoidance—some improvement in 3 mos.	BOP low diet—almost clearance of his facial and neck dermatitis
7	8 yrs	F	Yes	Hand and feet	For 6 mos vesicular hand and foot dermatitis	Nickel and cobalt	Multivitamins; Ballet leather shoes	Educated parent/patient on topical and dietary avoidance simultaneously.	Low nickel and cobalt diet, discontinue gummy multivitamins— Hand dermatitis cleared; Foot dermatitis 75% improvement in 4 wks after diet avoidance
8	16 yrs	M	Yes	Generalized, worse on palms and soles	Multiple flare up of his AD, for last couple of yrs vesicular hand dermatitis	Nickel and cobalt	Leather golf clubs' grip	On nickel avoidance plan for 6 yrs from pediatric dermatologist per parent.	Low nickel and cobalt diet—60% improvement after 6 wks of diet avoidance; occasional flares

BOP, balsam of Peru; PHP, personal health products; AD, atopic dermatitis; DMG test, dimethylglyoxime test.

TABLE 2. *High-Nickel Containing Foods*

Canned food
Shellfish
Chocolate
Oatmeal
Beans, lentils
Soy protein
Sesame seeds
Wheat bran cereals
Dates, figs, raspberries, pineapple
Baking powder in large amounts
Hazelnuts, peanuts, almonds
Vitamins containing nickel

TABLE 3. *Food Containing Balsam of Peru (23,42,43)*

Spices (vanilla, cloves, and cinnamon)
Citrus fruits
Chocolate
Sodas
Tomatoes and tomato-containing products (ketchup, BBQ sauce, salsa)
Chili
Flavored tea
Chewing gum
Ice cream
Flavoring agents
Wine, beer, gin
Cough remedies
Pickled vegetables

improvement. One of our patients, who presented with connubial dermatitis to BOP, was specifically found to have flares of her dermatitis with consumption of vanilla containing teething biscuits. Table 3 lists the foods known to flare BOP-allergic patients. Recently, Srivastava et al (27) confirmed finding BOP-based allergens, cinnamic alcohol, and coniferyl alcohol, in tomatoes.

Plants from the Compositae (Asteraceae) family have a potential to cause SCD in sensitized children. A significant number of children are reported to be sensitized to this group of plants, because of a global increase in the use of "natural" and "organic" products that contain sesquiterpene lactones (SL), the most common allergen (28). Ingestion or inhalation of a variety of different flowers, herbs, vegetables, and weeds that are part of this family (e.g., chamomile, *Echinacea*, marigold, mugwort, *Lactuca sativa* (lettuce), *Cynara scolymus* (globe artichoke), *Helianthus annuus* (sunflower)) may initiate a systemic reaction (29). Paulsen et al (30) demonstrated cross-reactivity between Compositae mix, colophonium and fragrance mix; thus patients with SCD should avoid ingestion of Compositae as well as flavorants- and BOP-containing foods.

Propolis, a wax resin produced by honeybees, is a potential cross-reactor with Compositae and BOP (31). It can be found in a wide range of products including cosmetics, lip balms, vitamins, coated oral pills, and cough syrups (32). In our series, patient 4 was diagnosed with SCD to cinnamic aldehyde (a BOP-associated fragrance) and propolis. Her dermatitis cleared with avoidance of her propolis-containing gummy multivitamins. Patients with SCD to propolis may also need to be advised of potential cross-reactivity with benzyl salicylate, benzyl cinnamate, fragrances, and Compositae.

Additives

Formaldehyde-sensitive patients have been reported to have SCD following aspartame ingestion (33). Aspartame is a widely used artificial sweetener present in a large number of diet products, as well as in some medicaments and vitamin supplements. Aspartame, after being ingested, is metabolized to phenylalanine, aspartic acid, and aspartic acid methyl ester in the intestinal wall, and later is further metabolized to methanol and transported to the liver (34). In the liver, methanol is oxidized to formaldehyde. Patient 5 was an asthmatic atopic with generalized SCD, who improved with topical avoidance and then had complete clearance when his monteleukast (Singulair™, Merck & Co., Inc., Whitehouse Station, NJ) chewable tablets (which contained aspartame) where substituted with the granule formulation. A trial of aspartame avoidance is reasonable in children with SCD and a positive patch test to formaldehyde.

Medicaments

While medications are one of the most commonly reported causes of SCD in the adult population (8,14,35,36), this phenomenon is far less reported in the pediatric population. In children, medicament-associated SCD has been reported following inhalation of mercury (5); oral and inhaled administration of thimerosal-containing antipneumococcal vaccine (4); oral administration of erythromycin (37), and homeopathic cough medicine (19,38) (see Table 4).

Management

We do not advise dietary avoidance universally, but reserve this therapy for patients thought to be exquisitely sensitive to certain allergens and those who demonstrate some improvement implementing topical avoidance regimens. Daily measurements for clinical improvements were not part of our protocol and we acknowledge that our intervals for observed clearance reflect patient-scheduled follow-up appointments.

TABLE 4. *Review Pediatric Cases of SCD in the Literature*

Reference	Age	Gender	History	HxAD	Patch-test result	Diagnosis	Causative Agent
Goossens et al (37)	18 mos	M	NS	–	LTT positive No PT Intradermal test + erythromycin	Baboon syndrome	Oral erythromycin
Nakayama et al (5)	6 yrs	F	1.5 yrs of erythematous vesicular lesions on hands Nummular and annular dermatitis	+	PT + thimerosal	SCD	Oral antipneumococcal (Lantigen B®, BexPharm, Seoul, Korea) vaccine daily for 2–3 wks. (Thimerosal as preservative)
Nakayama et al (5)	12 yrs	F	Erythematovesicular eruption + dyshidrotic hand eczema	+	PT + thimerosal	SCD	Nasal Thimerosal containing antipneumococcal vaccine
Lerch et al (40)	8 yrs	M	Flexural erythema of the large folds, the genital and gluteal area was present	+	PT + to phenylmercuric borate Mercury ammonium chloride thimerosal metallic mercury	Baboon syndrome	Mercury-containing lozenge for a pharyngitis
Lerch et al (40)	12 yrs	M	Erythroderma with disseminated Pustules	NS	PT + Phenylmercuric acetate and metallic mercury	Acute generalized exanthematous pustulosis (AGEP)	Metallic mercury
García-Menaya et al (41)	5 yrs	F	Erythematous and eczematous pruritic lesions localized in gluteal and inguinal region	NS	PT: mercury (+++) and thimerosal (++)	Baboon syndrome	Broken thermometer at home 2 days prior to rash
García-Menaya et al (41)	2 yrs	M	Erythematous and eczematous pruritic lesions localized in gluteal and inguinal region	NS	PT: mercury (+++) and thimerosal (++)	Baboon syndrome	Broken thermometer at home 2 days prior to rash
Audicana et al (19)	5 yrs	F	Itchy macular erythematous rash, symmetrically distributed in the anogenital area and thighs	NS	Prick test negative PT: thimerosal (++), metallic mercury (+++)	Baboon syndrome	History of neonatal periumbilical dermatitis associated with merbromin use on the cord. Single homeopathic tablet (Mercurius HeelAS), for cough

Hx AD: history of atopic dermatitis; NS, not specified; LTT, lymphocyte transformation test; PT, patch test.

The two most affected patients (1 and 5) were observed for longer than 6 weeks. We suspect that a 'reset' in the reactivity of the immune system takes a longer interval with increased clinical involvement. Furthermore, in certain cases, re-exposure to chemicals (or cross-reactants), for example via aerosolization by others (as in fragrances) (39), could result in a further delay of the 'reset' and thus extend the expected improvement well beyond 6 weeks even in the most compliant of patients.

SUMMARY

Systemic contact dermatitis may be more prevalent in U.S.-based pediatric populations than previously thought, and we recommend that it be considered in children diagnosed with ACD who demonstrate some improvement after allergen contact avoidance. Diet in children with SCD should be evaluated closely, and just high-content allergen foods be avoided without eliminating important nutritional aliments needed for children to grow. All medications—prescription, over-the-counter, alternative and complementary—should be reviewed for potential sources of exposure and safer substitutions made when possible. Per patient requests, once the dermatitis has cleared re-introduction of the 'favorite foods' may be performed in moderation and with monitoring. If the dermatitis returns (as many have with re-introduction), it is in the control of the patient/parent to reinstate the avoidance at the strictest level achievable to hold the dermatitis at bay.

CONFLICT OF INTEREST

This center is performing an Allerderm-sponsored PREA T.R.U.E. TEST clinical trial of panel 1.1, 2.1, and 3.1 in children and adolescents. The authors have no other financial disclosures to declare related to the content of this article.

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