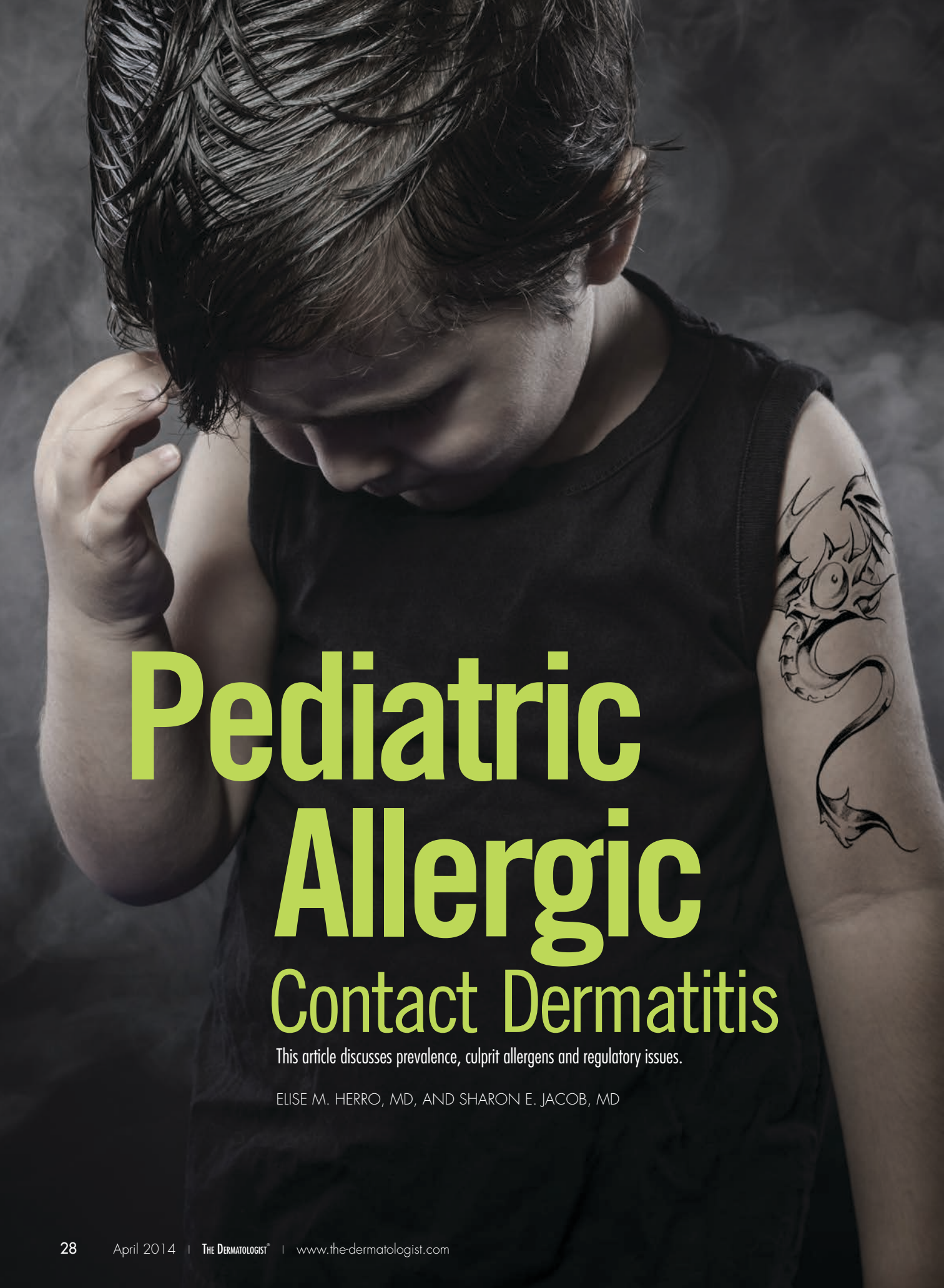

Pediatric Allergic Contact Dermatitis

This article discusses prevalence, culprit allergens and regulatory issues.

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Pediatric contact dermatitis has become an increasingly recognized entity in the last decade, with recent pediatric contact allergy estimates ranging from 41% to 77% in those referred for patch testing.[1] Reports of allergic contact dermatitis (ACD) in pediatric patients who were not necessarily confirmed by patch testing have also increased.

Car seat dermatitis, for example, has gained much attention recently; the clinical distribution of which corresponds to areas of contact with the infant-toddler seat (**Figure 1**). While an allergen has not been confirmed, it is thought to be related to the "shiny type of material" found in the seat pad.[2] The reaction may be either an irritant contact dermatitis or an ACD to a number of plausible allergens ranging from adhesives and resins to biocides and chemicals (such as dimethyl fumarate [DMF]), which is used as an "anti-mold" included with shipped goods. One note about DMF is that in March 2009, the European Commission banned the importation of goods that contained greater than the maximum allowable amount of DMF.[3] That said, DMF was designated as the Allergen of the Year in 2011 by the American Contact Dermatitis Society (ACDS) to bring awareness to the fact that it was still being used in overseas manufacturing and shipping worldwide.

Temporal associations can sometimes be made by the astute parent or clinician in lieu of patch testing. For example, Mussani et al reported a 3-year-old diagnosed as having systemic contact dermatitis (SCD) to topical application of clioquinol/hydrocortisone combination cream, which manifested clinically as baboon syndrome.[4] While baboon syndrome originally referred to symmetrical erythema of the gluteal area, involvement of flexural and/or intertriginous folds is now also recognized as forms of SCD.[5]

Figure 1. Car seat dermatitis has gained attention recently.

This particular patient's parents opted to have the clinician formulate their best guess as to the culprit and declined confirmatory patch testing, which has also been our clinical experience at times in pediatric contact dermatitis. The authors were able to make a correct assessment based on clinical exam and exposure history, as well as trial of avoidance. A provocative use test was parentally deferred in this patient, which also reflects our experience. It is more difficult to do the confirmatory provocation tests in pediatric patients (as opposed to adults), as many parents outright do not want their children to be again subjected to a potential flare of their dermatitis, once they have finally got them well. This case also points out the very realistic difficulty in patch testing where certain allergens, such as medications, may not be readily available for patch testing.

Another widely seen example of an allergen, which is often diagnosed in association with ACD cases without the confirmatory patch tests, is nickel, the ACDS 2008 Allergen of the Year. Nickel has been the most prevalent allergen found in patients of all ages for the last 3 decades at patch test centers worldwide.[3]

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Many patients can associate dermatitis of the earlobes with costume jewelry or infraumbilical dermatitis with jean snaps or belt buckles, and in these cases the history reveals the diagnosis. For example, Kaye et al described a case of SCD to nickel in 2012, in which a 10-year-old boy swallowed a Canadian quarter and then developed erythroderma and fever.[6] Because the quarter became lodged in the child's stomach lining, endoscopy was performed to remove the coin and the patient experienced a complete recovery. Confirmatory patch testing was deemed not medically necessary.

Figure 2. Coinage is only one of many items that contain nickel.

Notably, coinage is only one of many items that contain this ubiquitous sensitizer (**Figure 2**). In fact, the European Union issued a directive in July 2001 to regulate consumer nickel exposure, specifying that items intended to be in direct and prolonged contact with the skin could not release >0.5 μg nickel/

cm^2/week.[7] While this functioned to positively change the epidemiology of nickel allergy in Europe, further interventions are still called for, according to Thyssen et al: "Regulation is a toothless tiger if compliance is not appropriately checked and enforced."[7] That being said, regulations such as these have yet to even be established in the United States, but are desperately needed.

Likewise, another allergen warrants discussion, the antioxidant chemial used in hair dye, namely para-phenylenediamine (PPD). In 2006, the ACDS designated PPD the Allergen of the Year, as it was becoming increasingly apparent that exposure rates were on the rise. This was notably in association with its use in temporary tattooing in combination with henna, also known as "black henna." These products are often applied at fairs, amusements parks, local boardwalks and aboard cruise ships. PPD is added to increase the intensity and longevity of the tattoo, as well as expedite drying, but is responsible for causing potential "significant and lifelong sensitization." Unfortunately, the practice still persists and the age of exposure has been steadily and reportedly decreasing, with children as young as 30 months being reported to have had significant reactions.[8]

For this reason, in 2008, the ACDS and the American Academy of Dermatology issued a health advisory as a joint initiative. Since then, states such as New Jersey, Oklahoma and Florida have introduced legislation regarding "black henna tattoos."[8] Of note, there are only 5 chemicals that have been named by the US Consumer Product Safety Commission as "strong sensitizers" and PPD is one of them.[9]

In 2013, FDA issued a consumer warning regarding the health risks of "black henna."[10] And, a reporting hotline is now available. Unfortunately, the FDA requirement for labeling ingredients does not apply, as "black henna" is not sold commercially.[9,10]

Of note, Canada's Food and Drugs Act prevents the sale of "black henna" temporary tattoos, and both Europe and New Zealand have issued directives warning of the potential sensitization risks and/or made recommendations regarding PPD concentration.[8,11]

PATCH TESTING FOR ACD IN AFFECTED CHILDREN

The clinical condition of ACD, however, may be overlooked, when the exposure source is not as obvious as earlobe dermatitis or "black henna", which is especially true in those patients with chronic contact dermatitis, the very young and when it is a contributing factor in atopic dermatitis.[12,13] In these cases, patch testing may be the only way to determine the role of contact allergy.

A significant number of these children have been patch tested at many international centers, with positive patch test (PPT) reactions noted to a variety of chemicals/categories, including nickel, cosmetics, fragrances and preservatives.[12,14,15]

The clinical condition of ACD, however, may be overlooked, when the exposure source is not as obvious as earlobe dermatitis or black henna, which is especially true in those patients with chronic contact dermatitis, the very young and when it is a contributing factor in atopic dermatitis.

The first reported patch test studies in affected children in the United States were in 2008, confirming that ACD was equally prevalent in US children as it was in adults.[1,16] Patch testing was also confirmed to be both safe and efficacious in afflicted children.[1,16] In their study, the North American Contact Dermatitis Group (NACDG) found no significant difference in the frequency of at least 1 relevant PPT when comparing children (age 0-18 years) and adults.[16]

The majority of children reported to have been patch tested has occurred at tertiary care centers on patients who have been referred by dermatologists and allergists. Therefore, the rates of PPT reactions are significantly higher (41%-83%) than in unselected asymptomatic patients from the general population (13.5%-24.5%).[17]

Moreover, due to the distribution of patients in referral populations at US-based referral centers, a significant number of tested patients have been Caucasian and Hispanic, rather than Asian and African American, and thus the results may again not be representative of the prevalence of ACD in the general population.[17]

PEDIATRIC PATCH TESTING: METHODOLOGY AND TRENDS

Patch testing is considered the *gold standard* for the diagnosis of ACD in both children and adults, although the commercially available patch test device does not currently carry an FDA indication in children. Nonetheless, a recent study evaluating the efficacy and safety of the Thin-layer Rapid Use Epicutaneous Test (Mekos Laboratories A/S, Hillerød, Denmark) panels 1.1, 2.1 and 3.1 in children and adolescents age 6 to 18 concluded that the patch test device is efficacious and safe in the pediatric population.[18] Notably, this test received its initial biologics license from the FDA in 1994 for use in adults.

In both Europe and the United States, a significant number of referral centers that test children base their allergen selection on individual patient's history and clinical distribution of dermatitis, eliminating the placement of irrelevant patches. This type of individualized, comprehensive patch testing can prove cumbersome, and is often not readily accessible, which potentiates lower detection rates.[1]

It is important to note that the techniques for pediatric patch testing have been reviewed in detail.[19-23] For instance, in 2007, the German Contact Dermatitis Research Group published recommendations for patch testing in children, emphasizing the importance of allergen removal after 24 hours so as not to induce irritant reactions. They did, however, state that the same allergen test concentrations used in adults should be utilized, in support of previous studies.[17] Moreover, allergen reads were also encouraged at 48 hours and an additional delayed reading after 72 hours, as in adult populations.[23]

Current consensus is that testing can be performed in the same manner as in adults in children older than 12 years (adolescents).[24-28] On the other hand, in children <6 years of age, patch testing is usually reserved for cases with the highest index of suspicion. No-

tably, afflicted patients even <1 year old have been patch tested and found to have clinically relevant allergens.[1] Many have been tested with the individually directed comprehensive technique, so as to minimize unnecessary exposure and to adjust for the limited surface area for patch placement.[17] Furthermore, while many studies have shown an increasing prevalence of ACD through adolescence,[29-32] 3 studies from the European literature, ranging from 1998 to 2005, place emphasis on the peak sensitization being in those patients age 3 and younger.[22,33,34] In a recent Italian study, 200 children age 3 to 36 months were found to have at least 1 PPT reaction.[35]

Another challenge encountered when testing young children is the level of activity that children engage in, both during patch test placement and while patches are in place. Therefore, special attention to properly securing the patches is necessary.[36] Tools, such as games and videos, to distract children during application have been found to be helpful.[37]

CLINICAL RELEVANCE

As touched on previously, proper patch testing protocols and allergen selection can be vital to the proper diagnosis of ACD. In addition, interpretation and the assignment of relevance to PPT results are critical, because there may be only partial concordance between a PPT and ACD.[17]

A PPT reaction (also known as contact allergy) indicates that an individual is sensitized to a given chemical allergen. It is important to note that a PPT may or may not be the cause of the patient's dermatitis. As in adults, relevance is assigned by analyzing the PPT result against the patient's history, allergen exposures and sites of dermatitis. This requires knowledge of where the tested chemicals are found in one's environment. PPT may account for all, part of or none of the patient's active dermatitis. Many pediatric patch testing studies have yielded impressive results regarding relevance, with 1 study showing an 83% prevalence rate of PPTs in patients age 1 to 18 and 77% clinical relevance.[1]

ACD AND CULPRIT ALLERGENS

In another study between 2004 and and 2006, University of Miami investigators found that 95.6% of patients age 10 months to 16 years had at least 1 PPT reaction. Of note, 76.6% of these PPTs were of definite or probable clinical relevance.

Moreover, many of those with PPTs also carried a diagnosis of atopic dermatitis; however, this was not found to be statistically significant, given the referral bias.[38]

This study also compared the top 10 culprit allergens from their institution to those of the Mayo Clinic (adult, 1998-2000, and pediatric, 2000-2006 data),[39] the NACDG (adult and pediatric data, both 2001-2004)[16,40] and the Ottawan pediatric contact dermatitis data, 1996 to 2006.[13] Nickel was found to be the top allergen across all of these studies, with its clinical relevance as high as 26%.[16]

Additional allergens that were found across nearly all groups' top allergen lists included *Myroxylon pereirae*, cobalt chloride, neomycin sulfate, fragrance mix, gold sodium thiosulfate, thimerosal and formaldehyde.

The *Textbook of Clinical Pediatrics* provides a list of 20 allergens reported to be prevalent in children worldwide, some of which have been discussed in this article.[17] See **Table**.

Furthermore, Jacob et al recently reviewed all the North American based

Table. ALLERGENS IN CHILDREN[3,17,43]

Allergen	Description
Nickel	Metal – alloys (naturally in chocolate)
Cobalt	Metal – often alloy with nickel
Potassium dichromate	Metal – derived from chromium
Gold	Metal – precious
Neomycin sulfate	Topical antibiotic
Bacitracin	Topical antibiotic
Tixocortol pivalate (screen for hydrocortisone)	Corticosteroid (Class A)
Budesonide and triamcinolone	Corticosteroid (Class B)
Sorbitan sesquioleate	Emulsifier (water-in-oil)
Propylene glycol	Preservative, solvent/moistening agent
Lanolin	Emollient
Fragrance mix 1	Mix of 8 fragrances: cinnamic alcohol, cinnamic aldehyde, alpha-amylcinnamic alcohol, geraniol, hydroxycitronellal, eugenol, isoeugenol and oak moss absolute
Fragrance mix 2	Mix of 6 fragrances: lyral, citral, citronellol, farnesol, coumarin and hexyl cinnamic aldehyde
Myroxylon pereirae (balsam of Peru)	Fragrance/flavorant – tree resin (naturally cross reacts with chemicals in tomatoes/ketchup)
Compositae mix, sesquiterpene lactone, parthenolide	Daisy (ragweed) family allergens
Colophony	Fragrance/adhesive – distillation product of conifers
Cocamidopropyl betaine	Detergent, surfactant
p-tert-butylphenol formaldehyde resin	Adhesive and neoprene cement allergen
Carbamates	Rubber accelerator
Thiuram	Rubber accelerator
Para-phenylenediamine	Hair dye chemical, black henna tattoos
Disperse dyes (blue 106/124; yellow 3/9)	Aniline dye
Formaldehyde	Preservative
Quaternium-15	Preservative – formaldehyde releaser

studies and case reports and suggested a basic pediatric series, based on top prevalent allergens with the highest clinical relevance, many of which have been discussed in this article as well. [41,17]

CONCLUSION

ACD in children is a significant problem that should be a diagnostic consideration in patients with chronic dermatitis, regardless of an atopic designation.[42]

Evaluation includes a thorough history, analysis of clinical distribution of the dermatitis and when indicated, patch testing. Sensitization to many allergens implicated in ACD could potentially be avoided with the proper public health legislation in place.

The United States needs to adopt public health initiatives, such as the nickel directive in Europe and the prohibition on the sale of "black henna" in Canada. While organizations, such as the ACDS, strive to increase awareness of contact allergy, national policies, directives and regulations are vital to impacting sensitization rates in children. ■

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