Current Dermatology Reports (2023) 12:254–259
https://doi.org/10.1007/s13671-023-00409-5

REVIEW

Patch Testing in Atopic Children: Is There a Difference?

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Accepted: 18 October 2023 / Published online: 6 November 2023

Abstract

Purpose of Review Atopic dermatitis (AD) and allergic contact dermatitis (ACD) are common inflammatory conditions that disproportionately affect the pediatric patients. This article explores the relationship between ACD and AD in children and how these two conditions can coexist, though previously thought not to be possible.

Recent Findings Patients with AD are at an increased risk of developing ACD due to several risk factors including compromised skin barrier and increased sensitization to allergens due to frequent topical exposure. According to the Pediatric Contact Dermatitis Registry, relevant contact allergens in children with atopic dermatitis include nickel sulfate, bacitracin, fragrance mix I, Balsam of Peru, and formaldehyde.

Summary Dermatologists must be cognizant of ACD underdiagnosis in AD children. Patch testing can elucidate potential causes for dermatitis and can guide a more targeted treatment plan in our pediatric patients.

Keywords Allergic contact dermatitis · Atopic dermatitis · Children · Pediatric rashes

Introduction

Atopic dermatitis (AD) is the most common inflammatory skin condition in children. Up to 27% of children with AD are also affected by allergic contact dermatitis (ACD) [1]. Because ACD appears clinically similar to AD, children are frequently not evaluated for ACD with epicutaneous patch testing resulting in missed concomitant ACD leading to poorly controlled dermatitis and significant quality of life (QoL) disruptions. The barrier disruption seen in AD can lead to increased allergen penetration and sensitization which results in heightened immune responses [2]. Distinguishing between ACD and AD via patch testing can lead to optimal management and improved patient QoL.

Pathophysiology of AD

The pathophysiology of AD is due to skin barrier dysfunction, microbial dysbiosis, and immune responses [3]. AD is a heterogeneous disorder linked to genetic and environmental factors leading to the cycle of itch, followed by scratch which leads to the clinical findings of erythema, dryness, lichenification, and pigmentary alteration [4]. Genetic mutations in the filaggrin protein can lead to lipid barrier abnormalities, increased transepidermal water loss, and the promotion of proinflammatory cytokine expression [5]. Furthermore, children with a parent who has AD are three times more likely to develop AD [6].

AD is a complex interplay of the adaptive and innate immune system and is primarily Th2 driven. Inflammation is due primarily to upregulation of interleukins (IL-) 13 and 4 that have effects on AD severity including activation of the itch transmission signal and reducing epidermal barrier proteins [7]. Several treatments targeting Th2 cytokines in AD have been approved by the Food and Drug Administration (FDA).

Pathophysiology of ACD

ACD is a type IV delayed hypersensitivity reaction resulting in allergen-induced T-cell activation. The first phase of the pathogenesis of ACD is sensitization, when the body is first exposed to the allergen. Langerhans cells in the body process these haptens and subsequently activate T lymphocytes in the regional lymph nodes [8]. Recurrent exposure to the antigen (elicitation phase) is characterized

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by the activation of sensitized hapten-specific T-cells. Primed effector and memory T-cells mobilize in response to re-exposed allergens and lead to a cytokine induced cascade of localized inflammation [8]. This results in clinical symptoms of ACD including erythema, edema, and pruritus. It was previously thought that ACD is primarily a Th1 process [9] but recent studies demonstrate the pathophysiology of ACD is likely multimodal involving Th2 and Th17 in some studies [10].

Why Is ACD a Sequela of AD?

Studies suggest that AD patients may have an attenuated Th1 driven immune response to certain contact allergens [11•]. An unhealthy skin barrier in AD increases the risk of hapten penetration and subsequently increased likelihood of irritancy and contact sensitization [12]. Studies have shown patients with filaggrin mutations are more likely to have contact sensitization to metals due to increased penetration of metal allergens [13]. Loss of filaggrin therefore increases risk of contact dermatitis due to an impaired chelating ability of the skin [14, 15]. Filaggrin mutations along with Il-4 and Il-13 cytokines also lead to increased bacterial colonization of the skin and worsening severity of AD further disrupting the skin barrier [16].

Another risk factor of AD patients contributing to the development of ACD is the frequent exposure to over-the-counter products containing potential allergens including, topical antibiotics, topical anti-itch products, cleansers, and moisturizers. Regular use of these products with the intent of reducing symptoms of AD can lead to increased exposure to potential contact allergens in AD patients [17]. Common allergens seen in those with AD include fragrances, topical antibiotics, and formaldehyde releasing preservatives (FRPs) which are common ingredients found in topical remedies for AD [16].

Patch Testing ACD in AD: Indications and Pitfalls

Patch testing (PT), the gold standard for diagnosing ACD, should be considered in children with AD who meet these criteria [18]:

(i) No improvement or rebounding of dermatitis with topical therapy
(ii) Therapy-resistant hand eczema in working individuals
(iii) Before starting systemic immunosuppressants for dermatitis treatment
(iv) Patients with atypical or changing dermatitis distribution, such as lesions in the eyelids, head, neck, hand, foot, or perioral area
(v) Adolescent ACD
(vi) Children presenting with widespread nummular eczema

PT Considerations in Children with AD

PT can be deferred in stable, well-controlled, or mild AD.

Avoid PT during:

- AD flare-ups
- Active dermatitis involving sites of patch application
- Recent use of systemic immunosuppressive agents
- Recent ultraviolet therapy or excessive sun exposure
- Recent exposure to topical steroids on the back
- When there is limited access to a full complement of allergens to test [19]

Challenges in PT Interpretation for Children with AD

False negative reactions can occur due to immunosuppression.

- Flaring dermatitis over the PT site can be misdiagnosed as a positive reaction, leading to decreased sensitivity and specificity of the patch test [6]

Therefore, PT results must be interpreted with caution in children with AD, considering lower irritancy threshold, tendency for weaker reactions, and diminished contact sensitization [6].

Top Allergens in Children with AD

Studies performed recently have showed an increased prevalence of contact allergies in children with AD because there is increased awareness of ACD in AD children and more frequent PT in children with refractory AD [19]. The most common allergens that were identified in children with AD, according to the Pediatric Contact Dermatitis Registry, a multicenter registry established in 2017 with support of the Dermatology Foundation to track the changing prevalence of ACD in children, are discussed in Table 1.

Similar to previous studies, nickel is the most common allergen found in pediatric patients and is the most common cause of ACD worldwide [20•]. Nickel, along with cobalt, is ubiquitous in the United States in costume jewelry, toys, keys, and potentially certain foods leading to systemic contact dermatitis. Although a nickel avoidance diet can be recommended in a subset of adults with a positive PT to nickel, food restriction in children should be only considered in severe cases as systemic contact dermatitis is less common (needs a reference).

Table 1 Top allergens in children with AD according to the Pediatric Contact Dermatitis Registry [40]

Allergens	Top allergens in children with AD	Common sources of exposure
Metal	Nickel sulfate	Jewelry, toys, electronics, and belt buckles
Fragrances	Fragrance mixes I and II Balsam of Peru	Shampoos, conditioners, bodywash, and cosmetics
Antibiotics	Bacitracin Neomycin	Topical antibiotics
Preservatives	Formaldehyde and releasers MI/MCI	Personal care products, shampoos, conditioners, soaps, cleansers, steroid creams, topical steroids, and permanent press/wrinkle free clothing
Surfactant	Cocamidopropyl betaine	"Gentle," "no-tears" shampoos, and cleansers
Emollients	Lanolin/wool alcohol Propylene glycol	Aquaphor and greasy moisturizers and creams

Fragrance mixes I and II, Balsam of Peru, and hydroperoxides of limonene and linalool are frequently encountered fragrance allergens in cosmetics, personal products, candles, essential oils, and perfumes/colognes [21]. Although children may not necessarily be using these products directly, they may be exposed to these chemicals such as connubial contact with adults [21]. Products marketed as fragrance-free, hypoallergenic, or specifically for children with "sensitive skin" or "eczema," may still contain fragrances and other allergens; therefore, parents and caregivers should read product labels and conduct their own research to ensure that the personal care products they choose are suitable for their child's specific needs and any potential allergies [22].

Other common allergens found in children with AD include topical antibiotics such as bacitracin, neomycin, and polymyxin. These ingredients are common antibacterial agents found in topical first aid ointments, eardrops, and eyedrops. Use of topical antibiotics on an already compromised skin barrier increases the risk of sensitization in patients with AD. At the time of writing, mupirocin ointment is a safe alternative with low risks of topical sensitization due to its availability only as a prescription with less over the counter exposure as other topical antibiotics.

Cocamidopropyl betaine (CAPB) is a coconut oil derived surfactant advertised as a "no tears" gentle cleanser used for infants [23]. A 10-year retrospective study defines CAPB as the 8th most common allergen, yet it is found in over 50% of shampoos labeled as "hypoallergenic" [24]. CAPB is also found to be a more common allergen in children with AD than without, and this may be due to the increased exposure of "gentle" products that are purportedly better for sensitive skin.

Formaldehyde and its releasers (such as bronopol, quaternium-15, diazolidinyl urea, DMDM hydantoin, and imidazolidinyl urea) are used as preservatives and disinfectants in cosmetics, hair products, clothing, and some prescription skin products such as ketoconazole 2% shampoo [24]. Children with AD who commonly use prescription corticosteroids may be exposed to formaldehyde releasers as well as an emulsifier known as sorbitan sesquioleate [25].

Lanolin, a wool alcohol, is a fat-like substance secreted by sheep oil glands. It is found in topical moisturizers such as Aquaphor (Beiersdorf, Hamburg, Germany), used by and advertised to children with AD [26]. A retrospective analysis conducted in Dutch children with and without AD showed that children with AD were more likely to react to lanolin and fragrances [26]. A 2018 study reviewing different emollients for treating AD notes that there is limited evidence on the efficacy of lanolin's occlusive effects on improving AD symptoms [17]. While lanolin is not a strong sensitizer, it has the potential to cause ACD and should be avoided if there is evidence of contact sensitization.

Management of ACD in AD

It is important for dermatologists to maintain a high index of suspicion for ACD in atopic children who are experiencing persistent symptoms especially in the setting of a suspected exposure to a potential allergen. Chronic exacerbations of ACD may be misdiagnosed as AD, and therefore, there should be a low threshold to patch test to identify these allergens. PT is the only validated method of detecting ACD.

Various PT series are available for children depending on their age and size. For small children, a more limited series is recommended such as the Pediatric Baseline Series [27]. Older children with more available space for patch placement can use the full American Contact Dermatitis Society (ACDS) Core Series which includes 90 allergens [28] or the North American Contact Dermatitis Group (NACDG) Series [29]. The T.R.U.E. Test (Smart Practice, Phoenix, AZ) is a commercially available, preloaded patch test which includes 35 allergens and one negative control that is approved by the FDA for use in

Table 2 Limited pediatric patch test series

	T.R.U.E. Test [41]	Pediatric Baseline Series [28]	North American Pediatric Patch Test Series [29, 42]	Australian Pediatric Baseline Series [32]	European Pediatric Series [31]
Age	6–17 years old	6–18 years	6–12 years	> 6 years	> 6 years
Number of allergens	35 allergens and 1 control	38 allergens	20 allergens	30 allergens	21 allergens

children over 6 years of age (Table 2). While more convenient to use and apply, the T.R.U.E. test's limited allergen selection leads to missing almost 40% of relevant PT reactions [30]. However, this is often a reasonable screening step when comprehensive patch testing is not available.

Allergens in children may differ based on exposure around the world. Regionally specific patch series such as the European Academy of Allergy and Clinical Immunology baseline of 21 allergens (9 core and 12 supplemental) and Australia's baseline series containing 30 allergens are also available for pediatric populations [31, 32]. In general, it is our experience that comprehensive patch testing with appropriate use of supplemental series equates to an increased likelihood of detecting contact dermatitis in children [30].

Once potential allergens are identified, patients should be educated on avoidance techniques including resources to access safe alternative products. The ACDS Contact Allergen Management Program (CAMP) is a system designed to help patients and physicians identify personal care products that are free of ingredients found on PT [33]. Patients are provided personalized lists of products including brands and specific items that are safe for use and are provided information sheets on the positive allergens and common items that should be avoided.

It is important to note that in patients with concomitant AD, complete resolution of the symptoms may not always be achieved through allergen avoidance alone so topical steroids may be used for residual dermatitis. Systemic treatments may be used in severe dermatitis (including AD and ACD or both), and these may include oral steroids, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, biologics, and JAK inhibitors. The only FDA approved biologic for AD in children over 6 months of age is dupilumab which targets the IL-4 and IL-13 signaling cascade [34]. It has also demonstrated efficacy in treating ACD when allergen avoidance alone is inadequate or not possible [34].

JAK inhibitors, specifically topical ruxolitinib, oral abrocitinib, and oral upadacitinib have been approved for children 12 and older, with AD and may also show effectiveness in treating ACD [35]. Further research is essential to understand underlying mechanisms that may prove useful in patients with both conditions.

Limitations of Patch Testing in Children

It should be noted that when patch testing children with AD, there are several challenges that must be addressed. Due to the small anatomic area of the back in smaller children, patches can also be placed on the abdomen or thighs or serial testing with the most suspected allergens can be performed [36]. Children with an active flare on the back should not be tested due to the risk of angry back syndrome, a nonreproducible phenomenon due to a generalized hyperreactivity state of the skin [37]. Children with angry back syndrome should return for PT after their flare has resolved. Some methods commonly used to help clear the back include wet wraps after a bath, soaking, and smearing with topical steroids or using cyclosporine or prednisone at the lowest available dose [38••]. Irritant reactions can be mistaken for true positives especially in younger children (increased circulation and stratum corneum turnover) and increased absorption [39]. These reactions are identified by looking at localization of irritation to the rim of the patch and can be mitigated by using lower concentration of allergens and limited time of allergen occlusion (24 h in younger children instead of 48 h) [36].

Conclusions

This review article highlights the most up-to-date literature of ACD in pediatric AD patients. Despite previous beliefs that ACD and AD could not coexist, there is evidence that AD may be a risk factor for ACD and can be present simultaneously. These studies suggest that ACD is commonly underdiagnosed in children with AD and are infrequently referred for PT. However, children with AD who do undergo testing are more likely to have a positive patch test result than children without AD. According to studies, AD may lead to an increased risk of sensitization to certain allergens such as emollients, fragrances, and topical antibiotics which are commonly found in over the counter products marketed for children with AD. Considering how ACD can prolong disease course in children with AD, PT should be considered in the appropriate context. By identifying potential allergens and treating ACD, children with AD can potentially experience reduced disease severity and improved QoL.

Author Contribution Both authors contributed equally on this manuscript. Both authors contributed to the conception, drafting, editing, and final review of the manuscript.

Availability of Data and Materials Not applicable.

Compliance with Ethical Standards

Ethical Approval Not applicable.

Competing Interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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